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As filed with the Securities and Exchange Commission on June 18, 2018

Registration No. 333-

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM S-1
REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933

RHYTHM PHARMACEUTICALS, INC.
(Exact name of Registrant as specified in its charter)

Delaware	**2834**	**46-2159271**
(State or Other Jurisdiction of Incorporation or Organization)	(Primary Standard Industrial Classification Code Number)	(I.R.S. Employer Identification Number)

500 Boylston Street
11th Floor
Boston, MA 02116
(857) 264-4280
(Address, including zip code, and telephone number, including area code, of Registrant's principal executive offices)

Keith M. Gottesdiener, M.D.
Chief Executive Officer and President
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Please send copies of all communications to:

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Approximate date of commencement of the proposed sale to the public:
As soon as practicable after the effective date of this Registration Statement.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act, check the following box. o

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. o

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. o

If this Form is a post-effective amendment filed pursuant to Rule 462(d) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. o

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer" "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer o	Accelerated filer o	Non-accelerated filer ☒ (Do not check if a smaller reporting company)	Smaller reporting company o Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒

CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities to be Registered	Proposed Maximum Aggregate Offering Price(1)(2)	Amount of Registration Fee(3)
Common Stock, $0.001 par value per share	$172,500,000	$21,477

(1) Includes additional shares of common stock which the underwriters have the option to purchase in connection with this offering.

(2) Estimated solely for the purpose of calculating the registration fee pursuant to Rule 457(o) under the Securities Act of 1933, as amended.

(3) Calculated based on Rule 457(o) based on an estimate of the proposed maximum offering price.

The Registrant hereby amends this Registration Statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment which specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933, as amended, or until the Registration Statement shall become effective on such date as the Securities and Exchange Commission, acting pursuant to said Section 8(a), may determine.

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SUBJECT TO COMPLETION, DATED JUNE 18, 2018
Preliminary Prospectus

$150,000,000

Rhythm Pharmaceuticals, Inc.

Common Stock

Rhythm Pharmaceuticals, Inc. is offering $150,000,000 of shares of common stock in this offering.

Our common stock is listed on the Nasdaq Global Market under the symbol "RYTM." The last reported sale price of our common stock on the Nasdaq Global Market on June 15, 2018 was $32.60 per share. The final public offering price will be determined through negotiation between us and the lead underwriters in the offering and the recent market price used throughout the prospectus may not be indicative of the final offering price.

We are an "emerging growth company" as defined by the Jumpstart Our Business Startups Act of 2012 and, as such, we have elected to comply with certain reduced public company reporting requirements for this prospectus and future filings. Investing in our common stock involves risks. See "Risk Factors" beginning on page 15 of this prospectus before making a decision to invest in our common stock.

	Per Share	*Total*
Public Offering Price	*$*	*$*
Underwriting Discount and Commissions[(1)]	*$*	*$*
Proceeds, before expenses, to us	*$*	*$*

(1) We refer you to "Underwriting" beginning on page 216 for additional information regarding underwriter compensation.

We have granted the underwriters an option for a period of up to 30 days to purchase up to $22,500,000 of additional shares of common stock.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The underwriters expect to deliver the shares to purchasers on or about , 2018.

MORGAN STANLEY *BofA MERRILL LYNCH* *COWEN*
NEEDHAM & COMPANY

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We and the underwriters have not authorized anyone to provide any information or to make any representations other than those contained in this prospectus or in any free writing prospectuses we have prepared. We and the underwriters take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may provide you. We are offering to sell, and seeking offers to buy, shares of common stock only in jurisdictions where offers and sales are permitted. The information contained in this prospectus is accurate only as of the date of this prospectus, regardless of the time of delivery of this prospectus or of any sale of the common stock.

PROSPECTUS SUMMARY

This summary highlights information contained elsewhere in this prospectus and does not contain all of the information that you should consider in making your investment decision. Before investing in our common stock, you should carefully read this entire prospectus, including our financial statements and the related notes included elsewhere in this prospectus. You should also consider, among other things, the matters described under "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations," in each case appearing elsewhere in this prospectus. Unless otherwise stated, all references to "us," "our," "RYTM," "we," the "Company" and similar designations refer to Rhythm Pharmaceuticals, Inc. or our predecessor company, as the context may require. See "Corporate Background and Distribution."

Overview

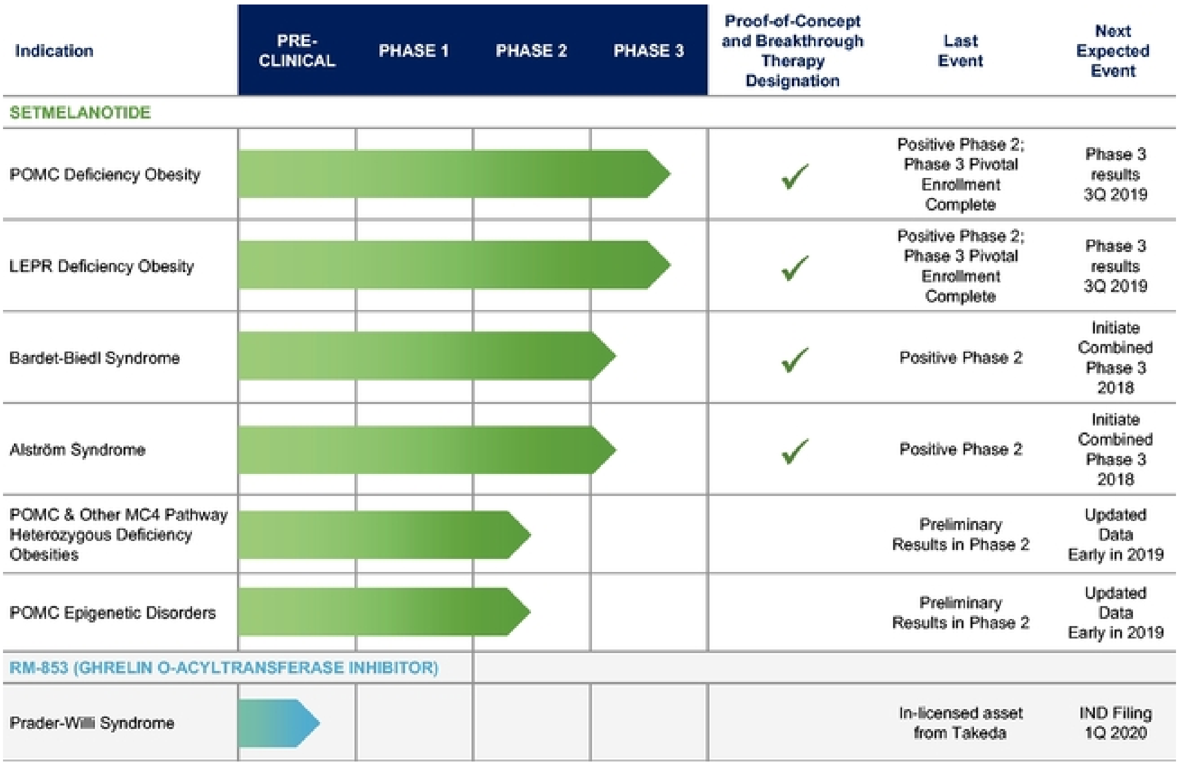
We are a biopharmaceutical company focused on the development and commercialization of therapeutics for the treatment of rare genetic disorders that result in severe, life-threatening metabolic disorders. Our lead product candidate is setmelanotide, a potent, first-in-class melanocortin-4 receptor, or MC4R, agonist peptide for the treatment of rare genetic disorders of obesity. We believe setmelanotide, for which we have exclusive worldwide rights, has the potential to serve as replacement therapy for the treatment of melanocortin-4, or MC4, pathway deficiencies. MC4 pathway deficiencies result in the disruption of satiety signals and energy homeostasis in the body, which, in turn, leads to intense feelings of hunger and to obesity. Our development efforts are initially focused on obesity related to six single gene-related, or monogenic, MC4 pathway deficiencies—pro-opiomelanocortin, or POMC, leptin receptor, or LepR, Bardet-Biedl syndrome, Alström syndrome, POMC heterozygous, and POMC epigenetic disorders—for which there are currently no effective or approved treatments. We believe that the MC4 pathway is a compelling target for treating these genetic disorders because of its critical role in regulating appetite and weight by promoting satiety and weight control, and that peptide therapeutics are uniquely suited for activating this target.

We have demonstrated proof of concept in Phase 2 clinical trials in POMC deficiency obesity, LepR deficiency obesity, Bardet-Biedl syndrome, and Alström syndrome, four genetic disorders of extreme and unrelenting appetite and obesity, in which setmelanotide dramatically reduced both weight and hunger. The U.S. Food and Drug Administration, or the FDA, has acknowledged the importance of these results by giving setmelanotide Breakthrough Therapy designation for the treatment of obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway. This designation currently covers four Breakthrough Therapy designation indications: POMC deficiency obesity, LepR deficiency obesity, Bardet-Biedl syndrome, and Alström syndrome. Setmelanotide is currently in Phase 3 development for POMC deficiency obesity and LepR deficiency obesity, and we are initiating a combined Phase 3 trial for Bardet-Biedl syndrome and Alström syndrome. We have completed enrollment in the pivotal cohorts for both our POMC deficiency obesity Phase 3 clinical trial and our LepR deficiency obesity Phase 3 clinical trial. We expect to report initial Phase 3 data from these trials in the third quarter of 2019, and subsequently plan to file for regulatory approval for these two indications concurrently. We believe that we have demonstrated proof of concept in our Phase 2 clinical trial in Bardet-Biedl syndrome and in Alström syndrome, and met with the FDA in May 2018 to discuss a combined pivotal Phase 3 clinical trial in these indications. Based on these preliminary discussions with the FDA, we currently plan to initiate this trial and enroll patients in 2018. We have an ongoing Phase 2 clinical trial in POMC heterozygous deficiency obesity and POMC epigenetic disorders. We reported initial, preliminary results in these additional Phase 2 indications in June 2018, and plan to provide a further update for these indications early in 2019. In total, approximately 300 obese subjects and patients have been treated with setmelanotide in previous and ongoing clinical trials in which setmelanotide demonstrated statistically significant weight loss with good tolerability.

Obesity is epidemic in the United States and current treatment approaches have demonstrated limited long-term success for most obese patients. We are taking a different approach to obesity drug development by leveraging new understanding of the genetic causes of severe obesity to develop innovative therapies that we believe have the potential for compelling efficacy. Setmelanotide's unique mechanism of action at MC4R enables a targeted approach to treating very severe obesity in patients with specific, monogenic defects in the MC4 signaling pathway. By restoring impaired function in this pathway, setmelanotide can serve as replacement therapy for genetic deficiencies, with the potential for dramatic improvements in weight and appetite. We believe we are at the forefront of improving treatment outcomes in subtypes of severe obesity that are caused by genetically-defined defects in the MC4 pathway.

Our Product Pipeline

The following chart depicts key information regarding the development of setmelanotide, including the indications we are pursuing within MC4 pathway deficiencies, the current state of development and our expected upcoming milestones:



Setmelanotide: A First-in-Class MC4R Agonist

Setmelanotide is a potent, first-in-class, MC4R agonist peptide administered by daily subcutaneous, or SC, injection. Setmelanotide activates MC4R, which is part of the key pathway that can independently regulate energy homeostasis, which refers to the body's energy balance, and appetite. The critical role of the MC4 pathway in weight regulation was validated with the discovery that single genetic defects along this pathway result in early onset and severe obesity. An expanding set of severe obesity genetic defects are now identified that involve genes in the pathway which are either upstream of MC4R —for example POMC deficiency obesity and LepR deficiency obesity—or genes that are downstream of MC4R or affect MC4R itself. We are focusing setmelanotide clinical development on patients with monogenic upstream genetic defects in which obesity is life-threatening but the downstream MC4 pathway is fully functional. We believe setmelanotide has the potential to restore lost activity in the MC4 pathway by bypassing the defects

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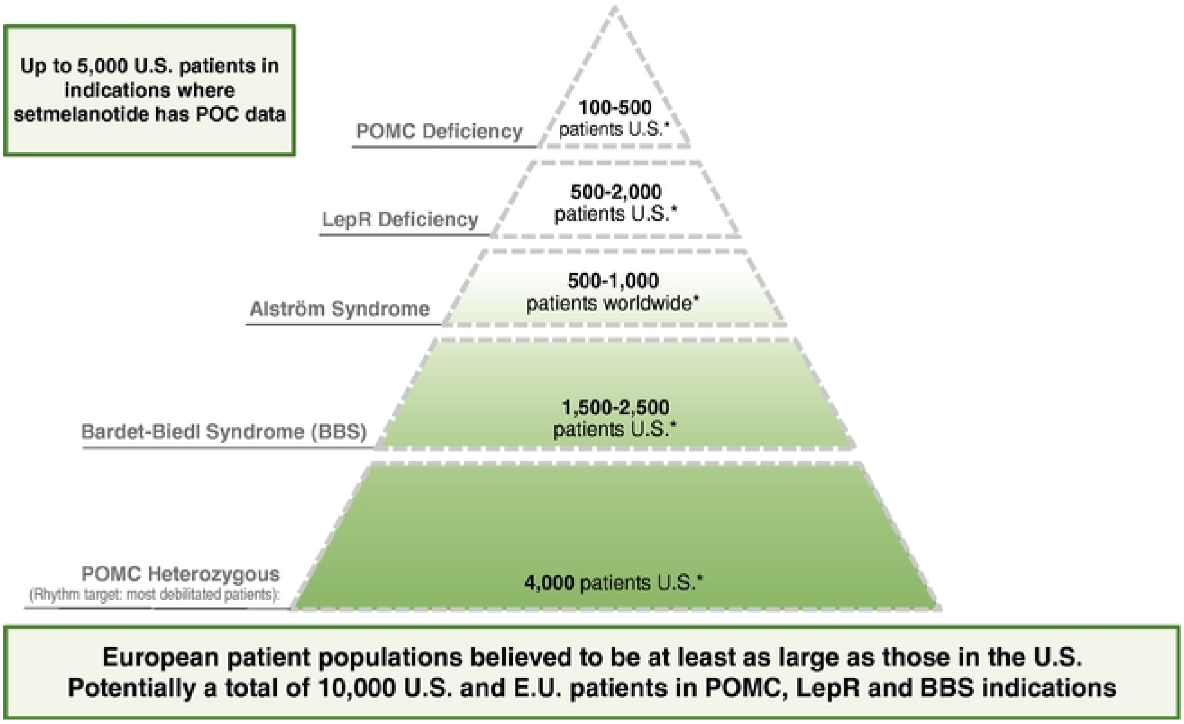
upstream of MC4R, and activating the MC4 pathway below such defects. In this way, setmelanotide may serve as replacement therapy to reestablish weight and appetite control in patients with these genetic disorders.

The first generation of MC4R agonists were predominantly small molecules that failed in clinical trials due to safety issues, particularly increases in blood pressure, in addition to having limited efficacy. In contrast, setmelanotide, a novel eight amino acid peptide, retains the specificity and functionality of the naturally occurring hormone that activates MC4R.

Clinical Development in Rare Genetic Disorders of Obesity Caused by MC4 Pathway Deficiencies

The figure below summarizes the indications on which we are focusing for the development of setmelanotide, including our clinical epidemiology estimates for the addressable patient populations within these indications.



* The patient numbers above are based on Company estimates from clinical publications.

† Epidemiological estimates are not yet available for POMC epigenetic disorders.

We have estimated the patient populations for our rare genetic disorders of obesity primarily by identifying patients or by estimating from clinical epidemiology information. Another method to estimate the size of these ultra-rare populations is by genetic epidemiology using newly available large genomic databases. Our preliminary genetic epidemiology estimates suggest a total of approximately 13,000 patients in the United States with POMC deficiency obesity and LepR deficiency obesity, representing a 5-fold increase relative to our clinical epidemiology based estimates. We believe the separate analyses that we have completed using clinical epidemiology and genetic epidemiology provide a robust range of patient population estimates for these rare disorders. However, to be conservative, we reference the clinical epidemiology figures in our descriptions of our target indications.

We believe that the patient populations in the European Union, or EU, are at least as large as those in the United States. However, we do not have comparable epidemiological data from the EU and these estimates are therefore based solely on applying relative population percentages to the Company-derived United States estimates described above.

POMC Deficiency Obesity

POMC deficiency obesity is a life-threatening, ultra-rare orphan disease, with approximately 50 patients reported to date. Ultra-rare orphan diseases are generally categorized as those that affect fewer than 20 patients per million. We estimate that our addressable patient population for this disorder is approximately 100 to 500 patients in the United States. Patients with POMC deficiency have unrelenting hunger, or hyperphagia, that begins in infancy and they develop severe, early onset obesity. POMC deficiency obesity results from two different homozygous genetic defects, both upstream of MC4R, that result in loss of function in the MC4 pathway. Currently, there is no approved treatment for the obesity and hyperphagia associated with this genetic disorder.

We have completed enrollment of the pivotal cohort in our Phase 3 open label, single arm, multinational trial to evaluate the safety and efficacy of setmelanotide for POMC deficiency obesity, with setmelanotide administered once daily by SC injection for 12 months, and we plan to report initial Phase 3 data in the third quarter of 2019. Previously, we completed a positive Phase 2 clinical trial in which two patients were enrolled and received treatment. These results were published in the New England Journal of Medicine in July 2016. The first patient in this trial lost 146.6 lbs. over 118 weeks, from a baseline weight of 341.7 lbs., and the second patient lost 89.3 lbs. over 64 weeks, from a baseline weight of 336.9 lbs. Both patients experienced substantial reductions in hunger, with hunger scores falling to one to two from baseline scores of nine to 10. Hunger scores were measured using a Likert score of zero to 10, where zero represents no hunger and 10 represents extreme hunger. Setmelanotide was generally well tolerated in this Phase 2 trial.

Leptin Receptor Deficiency Obesity

LepR deficiency obesity is an ultra-rare orphan disease that results in hyperphagia and severe early-onset obesity, with an estimated prevalence of 1% of subjects with severe, early-onset obesity. We estimate that our addressable patient population for this disorder is approximately 500 to 2,000 patients in the United States. Like other deficiencies upstream in the MC4 pathway, LepR deficiency results in loss of function in the MC4 pathway. Therefore, patients with this indication also manifest hyperphagia and severe obesity from early childhood. Currently, there is no approved treatment for the obesity and hyperphagia associated with LepR deficiency obesity.

We have completed enrollment of the pivotal cohort in our Phase 3 open label, single arm, multinational trial to evaluate the safety and efficacy of setmelanotide for LepR deficiency obesity, with setmelanotide administered once daily by SC injection for 12 months, and we plan to report initial Phase 3 data in the third quarter of 2019. Previously, we completed a positive Phase 2 clinical trial in which three patients were enrolled and received treatment in this trial each experiencing significant weight loss and substantial reductions in hunger. These results were published in Nature Medicine in May 2018. Setmelanotide was generally well tolerated in this Phase 2 trial.

Based on our POMC deficiency obesity and LepR deficiency obesity Phase 2 results, the FDA granted setmelanotide Breakthrough Therapy designation for the treatment of obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway, which includes both POMC deficiency obesity and LepR deficiency obesity, enabling an expedited path to approval of setmelanotide for these two indications. The FDA has granted orphan drug designation for setmelanotide for the treatment of POMC deficiency obesity and LepR deficiency obesity.

Bardet-Biedl Syndrome

Bardet-Biedl syndrome is a life-threatening, ultra-rare orphan disease with a prevalence of approximately one in 100,000 in North America. We estimate that our addressable patient population for Bardet-Biedl syndrome obesity is approximately 1,500 to 2,500 patients in the United States. Bardet-Biedl syndrome is a monogenic disorder that causes severe obesity and hyperphagia as well as vision loss, polydactyly, kidney abnormalities, and other signs and symptoms. Currently there are no approved or effective therapies for Bardet-Biedl syndrome.

We have demonstrated proof of concept based on data from five patients in our Phase 2 clinical trial in Bardet-Biedl syndrome, indicating that this is also a setmelanotide-responsive, upstream MC4 pathway disorder. Four of these five patients showed early, but significant weight loss and all five patients showed clear improvements in every hunger assessment. We reported preliminary Phase 2 results in the fourth quarter of 2017, and provided an update on these patients in the second quarter of 2018. Based on these results, the FDA recently included Bardet-Biedl syndrome under our existing Breakthrough Therapy designation for setmelanotide. Setmelanotide has been generally well tolerated in this trial.

Alström Syndrome

Alström syndrome is a life-threatening, ultra-rare orphan disease with a prevalence of approximately one in one million in North America. We estimate that our addressable patient population for Alström syndrome is approximately 500 to 1,000 patients worldwide. Alström syndrome is a monogenic disorder, closely related to Bardet-Biedl syndrome, that causes childhood obesity and hyperphagia as well as progressive vision loss, deafness, cardiomegaly, insulin resistance and other signs and symptoms. Currently there are no approved or effective therapies for Alström syndrome.

We believe we have recently demonstrated proof of concept in our Phase 2 clinical trial in Alström syndrome, indicating that this is also a setmelanotide-responsive, upstream MC4 pathway disorder. Based on these results, the FDA recently included Alström syndrome in our existing Breakthrough Therapy designation for setmelanotide. Setmelanotide has so far been generally well tolerated in this trial.

We met with the FDA in May 2018 to discuss a combined pivotal Phase 3 clinical trial in both Bardet-Biedl syndrome and Alström syndrome. Based on these preliminary discussions with the FDA, we currently plan to initiate this trial and enroll patients in 2018.

Other Upstream Genetic Defects in the MC4 Pathway

We are also focusing on additional monogenic, upstream MC4 pathway deficiencies for which setmelanotide can function as replacement therapy and provide activation of the pathway downstream of the defect, promoting satiety and weight control. We have enrolled patients in Phase 2 proof of concept trials for POMC epigenetic disorders, and for POMC heterozygous deficiency obesity, for which we estimate our addressable population is approximately 4,000 patients in the United States. For all of these patients, hyperphagia and obesity can have significant health consequences for which there is currently no approved treatment. We reported initial, preliminary results from these trials in the second quarter of 2018, and plan to provide a further update for these indications early in 2019.

Expanding Attention to the Diagnosis of Genetic Obesity

We are supporting several initiatives to expand the diagnosis of genetic obesity, including The Genetic Obesity Project. The Genetic Obesity Project has initiated a genotyping study, called GO-ID, and a patient registry, called TEMPO, both focusing initially on identifying people with POMC deficiency obesity and LepR deficiency obesity and which we intend to expand to include other MC4 pathway deficiencies. We will be expanding our panel of obesity-related genes used in our GO-ID study in the second half of 2018. The preliminary results, in 560 patients, from the GO-ID study suggest that patients with these disorders can be successfully identified. We are also conducting genetic obesity epidemiology analysis of MC4 pathway genetic defects in a large representative sample of the U.S. population, and we expect to expand the genetic databases in our research efforts on an ongoing basis.

RM-853: A Potent Ghrelin O-Acyltransferase Inhibitor

In addition to our development of setmelanotide, in April 2018, we announced that we had acquired exclusive, worldwide rights from Takeda Pharmaceutical Company Limited, or Takeda, to develop and commercialize T-3525770, now called RM-853. RM-853 is a potent, orally available ghrelin o-acyltransferase, or GOAT, inhibitor currently in preclinical development for Prader-Willi Syndrome, or PWS. PWS is a rare genetic disorder that results in hyperphagia and early-onset, life-threatening obesity, for which there are no approved therapeutic options. RM-853 is currently in pre-clinical development. We anticipate filing an Investigational New Drug application, or IND, for RM-853 with the FDA in 2020.

Company History

Our company was founded in November 2008 by former biopharmaceutical executives who have successfully developed, commercialized and in-licensed innovative pharmaceutical products, and we have subsequently expanded our senior management team to further broaden our team's experience in developing, registering and commercializing new drugs. In addition, our scientific advisory board, or SAB, members have extensive clinical expertise in obesity, endocrinology and metabolic diseases. We intend to leverage the experience of our senior management team and SAB to develop and commercialize setmelanotide. Through our senior management team's network of industry contacts, we will continue to evaluate additional product candidate licensing and acquisition opportunities.

Our setmelanotide patent portfolio includes composition of matter patents for setmelanotide that expire in the United States in 2027, with possible patent term extension to 2032 under the Hatch-Waxman Act. Additional patent coverage may be provided due to pending formulation patent applications, if such pending formulation applications were issued.

Our Strategy

Our goal is to be a leader in developing and commercializing targeted therapies for genetic deficiencies that result in life-threatening metabolic disorders. The key components of our strategy are:

- **Rapidly develop setmelanotide for rare genetic disorders of obesity caused by MC4 pathway deficiencies.** We are aiming to dramatically improve patient outcomes in severe obesity by targeting setmelanotide's mechanism of action to the treatment of patients with genetically-defined defects in the MC4 pathway. We are focusing setmelanotide clinical development on monogenic upstream genetic defects in which obesity is life-threatening but where the downstream MC4 pathway is fully functional.

- **Advance setmelanotide for POMC deficiency obesity and LepR deficiency obesity as our first indications in upstream MC4 pathway deficiencies.** We have completed enrollment of the pivotal cohorts in our Phase 3 trials in POMC deficiency obesity and LepR deficiency obesity, and plan to report initial data from these trials in the third quarter of 2019. We are working with the FDA, based on our Breakthrough Therapy designation, to prepare concurrent New Drug Application, or NDA, filings for these two indications as part of an expedited path to approval for POMC deficiency obesity and LepR deficiency obesity.

- **Advance setmelanotide for Bardet-Biedl syndrome and Alström syndrome as our second set of indications in upstream MC4 pathway deficiencies.** We have demonstrated proof of concept in Bardet-Biedl syndrome and Alström syndrome, indicating that these are also setmelanotide responsive, upstream MC4 pathway disorders. Based on these results, the FDA recently included these disorders under our existing Breakthrough Therapy designation for setmelanotide. In May 2018, we met with the FDA to discuss a combined pivotal Phase 3 clinical trial in both Bardet-Biedl syndrome and Alström syndrome. Based on these preliminary discussions with the FDA, we currently plan to initiate this trial and enroll patients in 2018.

- **Expand setmelanotide development to additional upstream MC4 pathway deficiencies, including POMC heterozygous deficiency obesity and POMC epigenetic disorders.** We believe we can leverage our experience with and mechanistic understanding of the MC4 pathway to advance development of setmelanotide for other upstream MC4 pathway deficiencies. We have an ongoing Phase 2 clinical trial that includes patients with these rare genetic disorders, and reported initial, preliminary results in these indications in June 2018. We continue to investigate other potential indications that may result from MC4 pathway deficiencies, in which we may study treatment with setmelanotide in the future.

- **Commercialize setmelanotide for rare disease indications in core strategic markets.** We intend to establish our own commercial sales and marketing organization in the United States and other core strategic markets. We expect this sales organization will target physicians treating these rare genetic disorders of obesity, including pediatric and adult endocrinologists. We believe that building our own commercial operations will deliver a greater return on our product investment than if we license the rights to commercialize these products to third parties. We may also selectively establish partnerships in markets outside the United States for sales, marketing, and distribution.

- **Leverage the broad experience of our team in clinical and commercial drug development, and product acquisitions.** We will apply our team's extensive experience in developing and commercializing innovative medicines to the development and launch of setmelanotide. We will apply similar expertise to advance our second product candidate, RM-853, from pre-clinical to clinical development. In addition, we intend to identify and acquire new pipeline product candidates in related diseases.

Risks Associated with Our Business

Our business is subject to a number of risks of which you should be aware before making an investment decision. These risks are discussed more fully in the "Risk Factors" section beginning on page 15 of this prospectus. These risks include the following:

- We are a development stage biopharmaceutical company with a limited operating history and have not generated any revenue from product sales. We have incurred significant operating losses since our inception, anticipate that we will incur continued losses for the foreseeable future and may never achieve profitability. As of March 31, 2018, we had an accumulated deficit of $126.7 million.

- Even if this offering is successful, we will need to raise additional funding, which may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate our product development efforts or other operations.

- We have only one product candidate in clinical development and we may not be successful in any future efforts to identify and develop additional product candidates.

- Positive results from early clinical trials of setmelanotide may not be predictive of the results of later clinical trials of setmelanotide. If we cannot generate positive results in our later clinical trials of setmelanotide, we may be unable to successfully develop, obtain regulatory approval for and commercialize setmelanotide.

- The number of patients suffering from each of the MC4 pathway deficiencies is small and has not been established with precision. If the actual number of patients with any of these conditions is smaller than we had estimated, our revenue and ability to achieve profitability will be materially adversely affected.

- Failures or delays in the commencement or completion of our planned clinical trials of setmelanotide could result in increased costs to us and could delay, prevent or limit our ability to generate revenue and continue our business.

- Changes in regulatory requirements, FDA guidance or unanticipated events during our clinical trials of setmelanotide may occur, which may result in changes to clinical trial protocols or additional clinical trial requirements, which could result in increased costs to us and could delay our development timeline. Additionally, it may be necessary to validate different or additional instruments for measuring subjective symptoms, and to show that setmelanotide has a clinically meaningful impact on those endpoints in order to obtain regulatory approval.

- Even if we complete the necessary clinical trials, the regulatory and marketing approval process is expensive, time consuming and uncertain and may prevent us from obtaining approvals for the commercialization of setmelanotide. We depend almost entirely on the success of setmelanotide, which is still in clinical development. We cannot be certain that we will be able to obtain regulatory approval for, or successfully commercialize setmelanotide. If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we will not be able to commercialize setmelanotide and our ability to generate revenue will be materially impaired.

- If we experience delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.

- Setmelanotide may cause undesirable side effects that could delay or prevent its regulatory approval, limit the commercial profile of an approved labeling or result in significant negative consequences following marketing approval, if any.

- Even if approved, reimbursement policies could limit our ability to sell setmelanotide.

- Competing products and technologies could emerge, adversely affecting our opportunity to generate revenue from the sale of setmelanotide.

- If we are unable to obtain and maintain patent protection for setmelanotide and its related technology, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize technology and products similar or identical to ours, and our ability to successfully commercialize our technology and setmelanotide may be impaired.

- Since we have only a limited history of operating as an independent company, we may incur unforeseen expenses associated with doing so.

Corporate Background and Distribution

We are a Delaware corporation organized in February 2013 under the name Rhythm Metabolic, Inc. and as of October 2015, under the name Rhythm Pharmaceuticals, Inc. See "*Corporate Background and Distribution*."

Our principal executive offices are located at 500 Boylston Street, 11th Floor, Boston, MA 02116, and our telephone number is (857) 264-4280. Our corporate website address is www.rhythmtx.com. Information contained on or accessible through our website is not a part of this prospectus, and the inclusion of our website address in this prospectus is an inactive textual reference only.

This prospectus contains references to our trademarks and to trademarks belonging to other entities. Solely for convenience, trademarks and trade names referred to in this prospectus, including logos, artwork and other visual displays, may appear without the ® or ™ symbols, but such references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights or the rights of the applicable licensor to these trademarks and trade names. We do not intend our use or display of other companies' trade names or trademarks to imply a relationship with, or endorsement or sponsorship of us by, any other companies.

Implications of Being an Emerging Growth Company

We are an "emerging growth company" as that term is used in the Jumpstart Our Business Startups (JOBS) Act of 2012 and, as such, have elected to comply with certain reduced public company reporting requirements. These reduced reporting requirements include reduced disclosure about Rhythm's executive compensation arrangements and no non-binding advisory votes on executive compensation. We will remain an emerging growth company until the earlier of (1) December 31, 2022, and (2) the last day of the fiscal year (a) in which we have total annual gross revenue of at least $1.07 billion, or (b) in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeds $700 million as of the prior June 30th, and (3) the date on which we have issued more than $1.0 billion in non-convertible debt during the prior three year period. We refer to the Jumpstart Our Business Startups Act of 2012 in this prospectus as the "JOBS Act," and references in this prospectus to "emerging growth company" shall have the meaning ascribed to it in the JOBS Act.

An emerging growth company may take advantage of reduced reporting requirements that are otherwise applicable to public companies. These provisions include, but are not limited to:

- the ability to present only two years of audited financial statements and only two years of related Management's Discussion and Analysis of Financial Condition and Results of Operations in this prospectus;
- an exemption from the requirements to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, as amended;
- reduced disclosure obligations regarding executive compensation in our periodic reports, proxy statements and registration statements; and
- exemptions from the requirement to hold a nonbinding advisory vote on executive compensation and to obtain stockholder approval of any golden parachute payments not previously approved.

We may use these provisions until such time as we cease to be an emerging growth company.

We have elected to take advantage of certain of the reduced disclosure obligations in the registration statement of which this prospectus forms a part and may elect to take advantage of other reduced reporting requirements in future filings. As a result, the information that we provide to our stockholders may be different from the information that you might receive from other public reporting companies in which you hold equity interests.

The JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. We have irrevocably elected not to avail ourselves of this exemption and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

THE OFFERING

Common stock offered by us	$150,000,000 of shares
Common stock to be outstanding after this offering	31,885,367 shares
Option to purchase additional common stock offered by us	Up to $22,500,000 of shares
Use of proceeds	We estimate that our net proceeds from this offering will be approximately $140.3 million at an assumed public offering price of $32.60 per share, which is the last reported sale price of our common stock on the Nasdaq Global Market on June 15, 2018, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. We intend to use the net proceeds from this offering, together with our existing cash resources, as follows: • approximately $42 million for the development of setmelanotide through the completion of our Phase 3 studies in POMC deficiency obesity and LepR deficiency obesity, as well as preparation for regulatory filing for these indications and initial preparation for the commercialization of setmelanotide in the United States; • approximately $10 million for the development of setmelanotide through the completion of our Phase 3 studies in Bardet-Biedl syndrome and Alström syndrome, as well as preparation for regulatory filing for these indications; • approximately $16 million to expand the clinical development of setmelanotide in new indications, including POMC heterozygous deficiency obesity and POMC epigenetics, as well as development of our once-weekly formulation of setmelanotide; • approximately $53 million for initiatives to expand the diagnosis of genetic obesity, including genetic sequencing of potential patients from targeted populations, expansion of our GO-ID study and TEMPO registry, research and scientific exchange related to our ongoing genotyping and genetic epidemiology studies; and • the balance to be used for other activities, including the preclinical development of RM-853 and general corporate purposes.
Risk factors	See "*Risk Factors*" beginning on page 15 and the other information included in this prospectus for a discussion of factors you should carefully consider before deciding to invest in our common stock.
Nasdaq Global Market Symbol	"RYTM"

The number of shares of our common stock to be outstanding after this offering is based on 27,284,140 shares of our common stock outstanding as of March 31, 2018, and assumes the sale of $150.0 million of shares of our common stock at an assumed offering price of $32.60, the last reported sale price of our common stock on the Nasdaq Global Market on June 15, 2018, and excludes:

- 223,544 shares of common stock issued to Takeda for the acquisition of the worldwide rights to develop and commercialize T-3525770, now called RM-853, on April 3, 2018;
- 38,150 shares of common stock issued upon the exercise of stock options after March 31, 2018 at a weighted average exercise price of $4.67 per share;
- 2,682,275 shares of common stock reserved for future issuance under our 2017 equity incentive plan, or the 2017 Plan, as of March 31, 2018;
- 272,841 shares of common stock reserved for future issuance under our 2017 employee stock purchase plan, as of March 31, 2018; and
- 2,427,629 shares of common stock issuable upon the exercise of stock options outstanding as of March 31, 2018 under our 2017 equity incentive plan at a weighted average exercise price of $11.85.

In this prospectus, unless otherwise indicated, the number of shares of common stock outstanding as of March 31, 2018 and the other information based thereon assumes no exercise by the underwriters of their option to purchase up to $22.5 million of additional shares of common stock and no exercise of the outstanding options described above.

SUMMARY FINANCIAL DATA

The following summary financial data for the years ended December 31, 2015, 2016 and 2017 are derived from our audited financial statements included elsewhere in this prospectus. The summary financial data as of March 31, 2018 and for the three months ended March 31, 2017 and 2018 have been derived from our unaudited financial statements included elsewhere in this prospectus. These unaudited financial statements have been prepared on a basis consistent with our audited financial statements and, in our opinion, contain all adjustments, consisting only of normal and recurring adjustments, necessary for a fair presentation of such financial data. You should read this data together with our audited financial statements and related notes included elsewhere in this prospectus and the information under the captions "Selected Financial Data" and "Management's Discussion and Analysis of Financial Condition and Results of Operations." Our historical results are not necessarily indicative of our future results, and our operating results for the three-month period ended March 31, 2018 are not necessarily indicative of the results that may be expected for the fiscal year ending December 31, 2018 or any other interim periods or any future year or period.

Our financial statements for the periods presented include allocations of costs from certain shared functions provided to us by the Relamorelin Company. These allocations were made based on either a specific identification basis or, when a specific identification is not practicable, a proportional cost allocation method which allocates expenses based on the percentage of employee time and research and development efforts expended on our business as compared to total employee time and research and development efforts, and have been included in our financial statements for the periods presented.

The financial statements included in this prospectus may not necessarily reflect our financial position, results of operations and cash flows as if we had operated as an independent company during all of the periods presented. See "*Corporate Background and Distribution*."

	Year Ended December 31, 2015	2016	2017	Three Months Ended March 31, 2017	2018
	(in thousands, except share and per share data)			(unaudited)	
Operating expenses:					
Research and development	$ 7,148	$ 19,594	$ 22,894	$ 4,873	$ 12,286
Selling, general and administrative	3,425	6,311	9,518	1,516	4,715
Total operating expenses	10,573	25,905	32,412	6,389	17,001
Loss from operations	(10,573)	(25,905)	(32,412)	(6,389)	(17,001)
Other income (expense):					
Revaluation of Series A Investor Right/Obligation and Investor Instrument	(500)	—	(1,863)	—	—
Interest income, net	—	33	566	29	542
Total other income (expense):	(500)	33	(1,297)	29	542
Net loss and comprehensive loss	$ (11,073)	$ (25,872)	$ (33,709)	$ (6,360)	$ (16,459)
Net loss attributable to common stockholders	$ (12,000)	$ (29,074)	$ (37,582)	$ (7,526)	$ (16,459)
Net loss attributable to common stockholders per common share, basic and diluted(1)	$ (1.18)	$ (2.85)	$ (2.83)	$ (0.74)	$ (0.60)
Weighted average common shares outstanding, basic and diluted	10,196,292	10,196,292	13,267,960	10,196,292	27,284,140

	As of March 31, 2018 Actual	As Adjusted(2)
	(in thousands) (unaudited)	
Balance Sheet Data:		
Cash, cash equivalents and short-term investments	$ 136,453	$ 276,713
Working capital	132,835	273,095
Total assets	139,443	279,703
Accumulated deficit	(126,711)	(126,711)
Total stockholders' equity	133,658	273,918

(1) See Note 2 within the notes to our financial statements appearing elsewhere in this prospectus for a description of the methods used to calculate basic and diluted net loss per share.

(2) As adjusted to reflect the issuance and sale of $150.0 million of shares of our common stock in this offering, at an assumed offering price of $32.60 per share, which was the last reported sale price of our common stock on the Nasdaq Global Market on June 15, 2018, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

CORPORATE BACKGROUND AND DISTRIBUTION

We are a Delaware corporation organized in February 2013 under the name Rhythm Metabolic, Inc. and as of October 2015, under the name Rhythm Pharmaceuticals, Inc. Prior to our organization and the Corporate Reorganization referred to below, we were part of Rhythm Pharmaceuticals, Inc., a Delaware corporation which was organized in November 2008 and which commenced active operations in 2010. We refer to this corporation as the Predecessor Company.

In March 2013, the Predecessor Company underwent a corporate reorganization, which we refer to as the Corporate Reorganization, pursuant to which all of the outstanding equity securities of the Predecessor Company were exchanged for units of Rhythm Holding Company, LLC, a newly-organized limited liability company, which we refer to as the LLC entity. After the consummation of this exchange and as part of the Corporate Reorganization, the Predecessor Company contributed setmelanotide and the MC4R agonist program to us and distributed to the LLC entity all of the then issued and outstanding shares of our stock. The result of the Corporate Reorganization was that we and the Predecessor Company became wholly-owned subsidiaries of the LLC entity and the two product candidates and related programs that were originally held by the Predecessor Company were separated, with relamorelin and the ghrelin agonist program being retained by the Predecessor Company and setmelanotide and the MC4R agonist program being held by us. We refer to the Predecessor Company after consummation of the Corporate Reorganization as the Relamorelin Company. The Predecessor Company filed the IND for setmelanotide in October 2011 and conducted the setmelanotide clinical trials up until the Corporate Reorganization, after which all clinical trials have been conducted by us.

In October 2014, the LLC entity granted to Actavis plc, now owned by Allergan, Inc., or Allergan, an exclusive option to acquire the Relamorelin Company. The transaction was limited to the acquisition of the Relamorelin Company and did not include our company. In October 2016, the option to acquire the Relamorelin Company was exercised and the sale to Allergan closed on December 15, 2016.

In August 2015, December 2015, January 2017 and August 2017, we sold 25,000,000 shares, 15,000,000 shares, 20,475,001 shares and 20,474,998 shares, respectively, of our series A convertible preferred stock to certain investors. Following the closing of our series A convertible preferred stock financings, the LLC entity remained our largest stockholder, with the balance of our stock being owned by our series A investors. In August 2017, the LLC entity exchanged 8,578,646 of its shares of our common stock for 78,666,209 newly-issued shares of our series A-1 junior preferred stock and the LLC entity distributed all of its shares of our series A-1 junior preferred stock to the holders of its preferred units and the remaining 1,617,646 shares of our common stock to the holders of its common units. We refer to the exchange and distribution as the Distribution. The series A-1 junior preferred stock converted into shares of our common stock on a 9.17-for-1 basis upon the closing of our IPO. Following the Distribution, the LLC entity did not own any of our common stock. In connection with our IPO, we effected a 1-for-9.17 reverse stock split on September 29, 2017.

On October 13, 2015, the Relamorelin Company changed its name to Motus Therapeutics, Inc. and we changed our name to Rhythm Pharmaceuticals, Inc.

We shared certain costs with the Relamorelin Company and effective December 2016 in connection with the sale of the Relamorelin Company we no longer share those costs.

RISK FACTORS

Investing in our common stock involves a high degree of risk. You should carefully consider the following risks and uncertainties, together with all other information in this prospectus, including our financial statements and related notes, before investing in our common stock. Any of the risk factors we describe below could adversely affect our business, financial condition or results of operations. The market price of our common stock could decline if one or more of these risks or uncertainties actually occur, causing you to lose all or part of the money you paid to buy our common stock. Additional risks that we currently do not know about or that we currently believe to be immaterial may also impair our business. Certain statements below are forward-looking statements. See "Cautionary Note Regarding Forward-Looking Statements" in this prospectus.

Risks Related to Our Financial Position and Need for Capital

We are a clinical-stage biopharmaceutical company with a limited operating history and have not generated any revenue from product sales. We have incurred significant operating losses since our inception, anticipate that we will incur continued losses for the foreseeable future and may never achieve profitability.

We are a clinical-stage biopharmaceutical company with a limited operating history on which to base your investment decision. Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. We were incorporated in February 2013 in connection with the Corporate Reorganization. Our operations to date have been limited primarily to acquiring rights to intellectual property, business planning, raising capital, developing our technology, identifying potential product candidates, undertaking preclinical studies and conducting research and development activities, including clinical trials, for setmelanotide. We have never generated any revenue from product sales. We have not obtained any regulatory approvals for setmelanotide.

Since our inception, we have focused substantially all of our efforts and financial resources on the research and development of setmelanotide, which is currently in Phase 3 clinical development for two indications, POMC deficiency obesity and LepR deficiency obesity, and in various phases of development for other indications. We have funded our operations to date primarily through capital contributions from the Predecessor Company, the Relamorelin Company and the LLC entity and proceeds from sales of preferred stock and have incurred losses in each year since our inception. See "*Corporate Background and Distribution.*"

Our net loss and comprehensive losses were $16.5 million and $6.4 million for the three months ended March 31, 2018 and 2017, respectively. As of March 31, 2018, we had an accumulated deficit of $126.7 million. Substantially all of our operating losses have resulted from costs incurred in connection with our development program and from general and administrative costs associated with our operations. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our stockholders' deficit and working capital. We expect our research and development expenses to significantly increase in connection with our additional clinical trials of setmelanotide and development of any other product candidates we may choose to pursue. In addition, if we obtain marketing approval for setmelanotide, we will incur significant sales, marketing and outsourced manufacturing expenses. We also will incur additional costs associated with operating as a public company. As a result, we expect to continue to incur significant and increasing operating losses for the foreseeable future. Because of the numerous risks and uncertainties associated with developing pharmaceutical products, we are unable to predict the extent of any future losses or when we will become profitable, if at all. Even if we do become profitable, we may not be able to sustain or increase our profitability on a quarterly or annual basis.

Our ability to become profitable depends upon our ability to generate revenue. To date, we have not generated any revenue from setmelanotide, and we do not know when, or if, we will generate any revenue. We do not expect to generate significant revenue unless and until we obtain marketing approval for, and begin to sell, setmelanotide. Our ability to generate revenue depends on a number of factors, including, but not limited to, our ability to:

- initiate and successfully complete later-stage clinical trials that meet their clinical endpoints;
- initiate and successfully complete all safety studies required to obtain U.S. and foreign marketing approval for setmelanotide as a treatment for obesity caused by genetic deficiencies affecting the MC4 pathway;
- successfully manufacture or contract with others to manufacture setmelanotide;
- commercialize setmelanotide, if approved, by building an internal sales force or entering into collaborations with third parties; and
- achieve market acceptance of setmelanotide in the medical community and with third-party payors.

Absent our entering into collaboration or partnership agreements, we expect to incur significant sales and marketing costs as we prepare to commercialize setmelanotide. Even if we initiate and successfully complete our pivotal clinical trials and setmelanotide is approved for commercial sale, and we incur the costs associated with these activities, setmelanotide may not be a commercially successful drug. We may not achieve profitability soon after generating product sales, if ever. If we are unable to generate product revenue, we will not become profitable and will be unable to continue operations without continued funding.

Even if this offering is successful, we will need to raise additional funding, which may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate our product development efforts or other operations.

We are currently advancing setmelanotide through clinical development. Developing peptide therapeutic products is expensive, and we expect our research and development expenses to increase substantially in connection with our ongoing activities, particularly as we advance setmelanotide in clinical trials. We intend to use the remaining proceeds from our IPO and from this offering primarily for the clinical development and regulatory approval of setmelanotide. Depending on the status of regulatory approval and, if approved, commercialization of setmelanotide, as well as the progress we make in the sale of setmelanotide, we may still require significant additional capital to fund the continued development of setmelanotide and our operating needs thereafter. We may also need to raise additional funds if we choose to pursue additional indications and/or geographies for setmelanotide or otherwise expand more rapidly than we presently anticipate.

Through August 2015, we received capital contributions from the Predecessor Company, the Relamorelin Company and the LLC entity. In August 2015, December 2015, January 2017 and August 2017, we raised aggregate gross proceeds of $25.0 million, $15.0 million, $20.5 million and $20.5 million, respectively, through our issuance of series A preferred stock. In October 2017 we completed our initial public offering, or IPO of 8,107,500 shares of common stock at an offering price of $17.00 per share, which included the exercise in full by the underwriters of their option to purchase up to 1,057,500 additional shares of common stock. We received gross proceeds of approximately $137.8 million, before deducting underwriting discounts, commissions and offering related transaction costs. As of March 31, 2018, our cash and cash equivalents and short-term investments were approximately $136.5 million. We expect our existing cash and cash equivalents and the proceeds from this offering will enable us to fund our operating expenses into the second half of 2020. However, our operating plan may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through public or private equity or debt financings, government or other third-party funding, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements, or a combination of these approaches. We will also require additional capital to obtain regulatory approval for, and to commercialize, setmelanotide. Raising funds in the current economic environment may present additional challenges. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or if we have specific strategic considerations.

Any additional fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize setmelanotide. In addition, we cannot guarantee that future financing will be available in sufficient amounts or on terms acceptable to us, if at all. Moreover, the terms of any financing may adversely affect the holdings or the rights of our stockholders and the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our shares to decline. The sale of additional equity or convertible securities would dilute all of our stockholders. The incurrence of indebtedness would result in increased fixed payment obligations and we may be required to agree to certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights, and other operating restrictions that could adversely impact our ability to conduct our business. We could also be required to seek funds through arrangements with collaborative partners or other third parties at an earlier stage than otherwise would be desirable and we may be required to relinquish rights to setmelanotide or technologies or otherwise agree to terms unfavorable to us, any of which may have a material adverse effect on our business, operating results and prospects.

If we are unable to obtain funding on a timely basis, we may be required to significantly curtail, delay or discontinue one or more of our research or development programs or the commercialization of setmelanotide or be unable to expand our operations or otherwise capitalize on our business opportunities, as desired, which could materially adversely affect our business, financial condition and results of operations.

Our very limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

We are an early-stage company. The Predecessor Company commenced active operations in February 2010, and we were incorporated as a separate company in February 2013. Our operations to date have been limited primarily to acquiring rights to intellectual property, business planning, raising capital, developing our technology, identifying potential product candidates, undertaking preclinical studies and, beginning in November 2010, conducting clinical trials. We have not yet demonstrated our ability to successfully complete a pivotal Phase 3 clinical trial, obtain marketing approvals, manufacture at commercial scale, or arrange for a third party to do so on our behalf or conduct sales, marketing and distribution activities necessary for successful product commercialization. Consequently, any predictions made about our future success or viability may not be as accurate as they could be if we had a longer operating history.

In addition, as a new business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. We will need to transition at some point from a company with a research and development focus to a company capable of supporting commercial activities and we may not be successful in such a transition.

We expect our financial condition and operating results to continue to fluctuate significantly from quarter-to-quarter and year-to-year due to a variety of factors, many of which are beyond our control. Accordingly, you should not rely upon the results of any quarterly or annual periods as indications of future operating performance.

Our historical financial information is not necessarily representative of the results we would have achieved as an independent company, and may not be a reliable indicator of our future results.

The historical financial information we have included in this prospectus may not reflect what our results of operations, financial position and cash flows would have been had we been an independent company during the periods presented. This is primarily because:

- our historical financial information reflects allocations for services historically provided to us by the Predecessor Company and the Relamorelin Company, which allocations may not reflect the costs we now and in the future will incur for similar services as an independent company; and

- our historical financial information does not reflect changes that we have incurred and expect to continue to incur as a result of operating as an independent company and from reduced economies of scale, including changes in cost structure, personnel needs, financing and operations of our business.

Risks Related to the Development of Setmelanotide

Positive results from early clinical trials of setmelanotide may not be predictive of the results of later clinical trials of setmelanotide. If we cannot generate positive results in our later clinical trials of setmelanotide, we may be unable to successfully develop, obtain regulatory approval for, and commercialize setmelanotide.

Positive results from any of our Phase 1 and Phase 2 clinical trials of setmelanotide may not be predictive of the results of later clinical trials. The duration of effect of setmelanotide tested in our Phase 1 and Phase 2 clinical trials was often for shorter periods than in our current pivotal Phase 3 clinical trials. The duration of effect of setmelanotide has only been studied in long-term durations for a small number of patients in our Phase 2 clinical trials and safety or efficacy issues may arise when more patients are studied in longer trials. It is possible that the effects seen in short-term clinical trials will not be replicated in long-term or larger clinical trials. In addition, not all of our trials demonstrated statistically significant weight loss and there can be no guarantee that future trials will do so.

Positive results for one indication are not necessarily predictive of positive results for other indications. We have demonstrated proof of concept in Phase 2 clinical trials in POMC deficiency obesity, LepR deficiency obesity, and Bardet-Biedl syndrome, three genetic disorders of extreme and unrelenting appetite and obesity, in which setmelanotide dramatically reduced both weight and hunger. We believe we have also demonstrated preliminary proof of concept in Phase 2 for Alström syndrome. We hypothesize that patients with other upstream genetic defects in the MC4 pathway may also respond with reductions in weight and hunger after treatment with setmelanotide, however patients with other upstream genetic defects may not have a similar response to setmelanotide, and until we obtain more clinical data in other genetic defects, we will not be sure that we can achieve proof of concept in such indications. In addition, while we believe that proof of concept in Bardet-Biedl syndrome and Alström syndrome has been demonstrated by improvements in hunger and weight reduction, supporting that this is a setmelanotide-responsive, MC4 pathway disorder, the results of this trial are still at a preliminary stage.

We have and will continue to have multiple clinical trials of setmelanotide ongoing, which are designed to include multiple genetically and clinically defined populations under one investigational protocol, although each population is enrolled and analyzed separately. A "basket" trial design could potentially decrease the time to study new populations by decreasing administrative burden, however, these trials may not provide opportunities for acceleration, and do not overcome limitations to extrapolating data from the experience in one disease to other diseases, because safety and efficacy results in each indication are analyzed separately. Accordingly, clinical success in a basket trial, or any trial in one indication, may not predict success in another indication. In contrast, in the event of an adverse safety issue, clinical hold, or other adverse finding in one or more indications being tested, such event could adversely affect our trials in the other indications and may delay or prevent completion of the clinical trials.

Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in later stage clinical trials after achieving positive results in early stage development, and we cannot be certain that we will not face similar setbacks. These setbacks have been caused by, among other things, pre-clinical findings made while clinical trials were underway. However, we have completed the key toxicology studies that the U.S. Food and Drug Administration, or the FDA, will require for our first approval, and which we believe the European Medicines Agency, or EMA, will require for authorization, which include, among others, chronic toxicity studies, reproductive and developmental toxicity studies, and juvenile toxicology studies. Based on the totality of animal testing results to date, including the lack of any observed genotoxicity or tissue proliferative activity of setmelanotide in chronic toxicity studies, the FDA has agreed to permit us to defer carcinogenicity studies until after approval of a new drug application, or NDA, for setmelanotide. Accordingly, we believe that we will be able to defer the submission of all carcinogenicity studies until after we receive regulatory approval to market setmelanotide in the U.S. While we believe this also to be true for the EMA, the EMA has not yet provided firm guidance on the need for carcinogenicity studies and accordingly, there can be no guarantee that we will be able to achieve this deferral which could impact the timing of any potential European Union, or EU, approval.

In addition to the foregoing issue, the FDA has requested that in our chronic rat and monkey studies we re-assess certain cells in brain, renal and liver tissues for the presence of vacuoles, which are common membrane-bound compartments. The recommendation was based on the FDA's review of a summary of a monkey study that noted the presence of macrophage aggregates, which are groupings of specific white blood cells, in the choroid plexus, a network of blood vessels and epithelial tissue in the membrane lining outside the brain and spinal cord. The FDA noted that the existence of macrophage aggregates appears to be related to the polyethylene glycol, or PEG, vehicle in the product, rather than setmelanotide itself. A similar question was raised by the competent authorities in France, in connection with the use of PEG in products for younger pediatric indications, and in discussion of our Pediatric Investigational Plan, or PIP. Based on this, we performed this re-assessment, which confirmed that no additional findings were present in any monkey tissues, but which did find a very small number of rats with vacuolated epithelial cells, or brain surface lining cells, in the choroid plexus of minimal severity that also appeared to be related to the PEG vehicle. We do not believe these findings raise any important safety concerns, in part because of the minimal severity, the localization of these aggregates, the lack of any adverse histopathological changes, and the lack of findings in other tissues. However, neither the FDA nor regulatory agencies in the EU has indicated that they agree with our position. In addition, we anticipate the EMA may request additional mechanistic studies to better understand these findings. It is also possible the FDA may require us to reflect these findings in the toxicological portion of the product labeling, and this may delay study in the youngest pediatric patients in some EU member states, such as France.

Additionally, setbacks may be caused by new safety or efficacy observations made in clinical trials, including previously unreported adverse events. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials nonetheless failed to obtain FDA approval or European Commission authorization. If we fail to obtain positive results in our Phase 3 clinical trials of setmelanotide, the development timeline and regulatory approval and commercialization prospects for setmelanotide and, correspondingly, our business and financial prospects would be materially adversely affected.

The number of patients suffering from each of the MC4 pathway deficiencies we are targeting is small and has not been established with precision. If the actual number of patients is smaller than we estimate, our revenue and ability to achieve profitability may be materially adversely affected.

Due to the rarity of our target indications, there is no comprehensive patient registry or other method of establishing with precision the actual number of patients with MC4 pathway deficiencies. As a result, we have had to rely on other available sources to derive clinical prevalence estimates for our target indications. Since the published epidemiology studies for these genetic deficiencies are based on relatively small population samples, and are not amenable to robust statistical analyses, it is possible that these projections may significantly exceed the addressable population, particularly given the need to genotype patients to definitively confirm a diagnosis.

Based on clinical epidemiology, we have estimated the potential addressable patient populations with these MC4 pathway deficiencies based on the following sources and assumptions:

- *POMC Deficiency Obesity.* There are approximately 50 patients with POMC deficiency obesity noted in a series of published case reports, each mostly reporting a single or small number of patients. However, we believe our addressable patient population for this deficiency may be approximately 100 to 500 patients in the United States, and a comparable addressable patient population in Europe, as most of the reported cases are from a small number of academic research centers, and because genetic testing for POMC deficiency is often unavailable and currently is rarely performed. Based on discussions with experts in rare diseases, we also believe the number of diagnosed cases could increase several-fold with increased awareness of this deficiency and the availability of new treatments.

- *LepR Deficiency Obesity and POMC Heterozygous Deficiency Obesity.* Our addressable patient population estimate for LepR deficiency obesity is approximately 500 to 2,000 patients in the United States, and for POMC heterozygous deficiency obesity is approximately 4,000 patients in the United States, with a comparable addressable patient population for both indications in Europe. Our estimates are based on:

  - epidemiology studies on LepR deficiency and POMC heterozygous deficiency in small cohorts of patients comprised of children with severe obesity and adults with severe obesity who have a history of early onset obesity;

  - U.S. Census Bureau figures for adults and children, and Centers for Disease Control and Prevention, or CDC, prevalence numbers for severe adult obese patients (body mass index, or BMI, greater than 40 kg/ m^2) and for severe early onset obese children (99th percentile at ages two to 17 years old); and

  - with wider availability of genetic testing expected for LepR deficiency and POMC heterozygous deficiency and increased awareness of new treatments, our belief that up to 40% of patients with these disorders may eventually be diagnosed.

Using these sources and assumptions, we calculated our estimates for addressable populations by multiplying (x) our estimate of the number of patients comprised of children with severe obesity and our estimate of a projected number of adults with severe obesity who have a history of early onset obesity, (y) the estimated prevalence from epidemiology studies of approximately 1% for LepR deficiency and 2% for POMC heterozygous, and (z) our estimated diagnosis rate of up to 40%.

- *Bardet-Biedl Syndrome.* Our addressable patient population estimate for Bardet-Biedl syndrome is approximately 1,500 to 2,500 patients in the United States based on:

  - published prevalence estimates of one in 100,000 in North America, which projects to approximately 3,250 people in the United States. We believe the majority of these patients are addressable patients; and

  - our belief that with wider availability of genetic testing expected for Bardet-Biedl syndrome and increased awareness of new treatments, the number of patients diagnosed with this disorder will increase.

- *Alström Syndrome.* Our addressable patient population estimate for Alström syndrome is approximately 500 to 1,000 patients worldwide. This estimate is based on:

  - published prevalence estimates of one in 1,000,000 in North America, which projects to approximately 325 people in the United States. We believe the majority of these patients are addressable patients; and

  - our belief that with wider availability of genetic testing expected for Alström syndrome and increased awareness of new treatments, the number of patients diagnosed with this disorder will increase.

- *POMC Epigenetic Disorders.* There is currently no epidemiology data that defines the prevalence of POMC epigenetic disorders.

We believe that the patient populations in the EU are at least as large as those in the United States. However, we do not have comparable epidemiological data from the European Union and these estimates are therefore based solely on applying relative population percentages to the Company-derived estimates described above.

We are conducting additional clinical epidemiology studies to strengthen these prevalence projections. In parallel, we have developed a patient registry for diagnosed patients with POMC deficiency and LepR deficiency (and other genetic disorders of obesity) which will further inform prevalence projections for these rare genetic orders.

Another method to estimate the size of these ultra-rare populations by genetic epidemiology is using newly available large genomic databases, containing full genome sequencing or exome sequencing. Ultra-rare orphan diseases are generally categorized as those that affect fewer than 20 patients per million. We have begun some substantial efforts with a series of such databases and/or collaborators. Our initial work has been with a database of approximately 140,000 genomes, which is representative of the U.S. population. These efforts generally are based on the prevalence of heterozygous mutations, as true null mutations are ultra-rare, and then standard scientific methods such as the Hardy-Weinberg equilibrium calculations, are applied to estimate the prevalence in the U.S. population. These methods make assumptions that may not be sufficiently robust for ultra-rare genetic disorders, and have the inherent variability of estimates for rare events.

In addition, the databases currently available only provide limited clinical data, such as, age, weight and BMI, that would be needed to associate genetic defects with severe obesity. Our continued investigations support that the genetic epidemiological estimates are larger than the clinical epidemiological estimates, but we will likely need to reconcile the scientific definition of mutations with the regulatory definition.

We believe the separate analyses that we have completed using clinical epidemiology and genetic epidemiology provide a robust range of patient population estimates for these rare disorders. However, to be conservative, we reference the clinical epidemiology figures in our descriptions of our target indications.

In addition, if any approval that we obtain is based on a narrower definition of these patient populations than we had anticipated, then the potential market for setmelanotide for these indications will be smaller than we originally believed. In either case, a smaller patient population in our target indications would have a materially adverse effect on our ability to achieve commercialization and generate revenues.

If the actual number of patients suffering from each of the MC4 pathway deficiencies we are targeting is smaller than we estimate or if any approval that we obtain is based on a narrower definition of these patient populations, including pediatric populations, our ability to recruit patients to our trials may be materially adversely affected.

If the actual number of patients with any of the MC4 pathway deficiencies we are targeting is lower than we believe, it may be difficult to recruit patients, and this may affect the timelines for the completion of clinical trials. If we experience delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could also be delayed or prevented.

The pediatric population is an important patient population for setmelanotide and our addressable patient population estimates include pediatric populations. However, it may be more challenging to conduct studies in this population, and to locate and enroll pediatric patients. Additionally, it may be challenging to ensure that pediatric or adolescent patients adhere to clinical trial protocols.

We currently are treating patients 12 years of age and older in our trials, and have started treating patients six to 11 years of age. Our aim is to gain regulatory approval and labeling for patients six years of age and older. We have received permission from the FDA and other equivalent competent authorities in the EU member states to enroll these younger patients, aged six to 11, in our pivotal trials. However, there may be issues that preclude the ultimate approval and labeling including, but not limited to, potential disagreement on dose titration, or delivery methods for small doses, or the suitability of patient reported outcomes in younger patients, the clinical endpoints in rapidly growing patients, as well as avoiding over-suppression of normal appetite in adolescents. In addition, the competent authorities in the EU member states may consider the polyethylene glycol vehicle in the product to carry additional risks in pediatric patients, and may look to new formulations, such as our once-weekly formulation, as being more suitable to younger pediatric patients. We also may not have one-year clinical data in six to 11 year old patients at the time of the POMC NDA filing, if we begin recruiting six to 11 year old patients into our pivotal trials, though we can provide one-year clinical data when it becomes available. We cannot predict if the FDA or other equivalent competent authorities in the EU member states will approve setmelanotide in younger pediatric patients, nor provide an estimate for the timing for approval, if any, for the use of setmelanotide for such patients. Furthermore, if the FDA or other equivalent competent authorities in the EU member states do not approve the use of setmelanotide in this population, the product candidate will not be labeled for promotion for these patients, even if they approve an NDA for setmelanotide for patients 12 and older.

While we have no knowledge of competitors developing product candidates intended to treat upstream MC4 pathway deficiencies, other than Prader-Willi-Syndrome, competitors may emerge. If that were to occur and competitors initiated clinical trials for product candidates that treat the same indications as setmelanotide, patients who would otherwise be eligible for our clinical trials may instead enroll in the clinical trials of our competitors' product candidates, and could impact our commercial success.

Patient enrollment is also affected by other factors including:

- the severity of the disease under investigation;
- the eligibility criteria for the clinical trial in question;
- the perceived risks and benefits of the product candidate under study;
- the success of efforts to facilitate timely enrollment in clinical trials;
- the patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment; and
- the proximity and availability of clinical trial sites for prospective patients.

Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays, could require us to abandon one or more clinical trials altogether and could delay or prevent our receipt of necessary regulatory approvals. Enrollment delays in our clinical trials may result in increased development costs for setmelanotide, which would cause the value of our company to decline and limit our ability to obtain additional financing.

Failures or delays in the commencement or completion of our planned clinical trials of setmelanotide could result in increased costs to us and could delay, prevent or limit our ability to generate revenue and continue our business.

We completed Phase 2 clinical trials for setmelanotide in 2016 for POMC deficiency obesity and are currently advancing an ongoing pivotal Phase 3 clinical trial for setmelanotide for POMC deficiency obesity. We completed Phase 2 clinical trials for setmelanotide for LepR deficiency obesity, and are currently advancing an ongoing pivotal Phase 3 clinical trial for setmelanotide in LepR deficiency obesity. These trials are overlapping in timing and duration and we plan to discuss with the FDA and other regulatory agencies, and will likely file concurrent NDAs for these two indications, which would have an impact on NDA timing and complexity.

We believe we have demonstrated proof of concept in Bardet-Biedl syndrome and Alström syndrome, are in ongoing discussions with the FDA to plan a pivotal Phase 3 clinical trial in Bardet-Biedl syndrome, likely combined with a pivotal Phase 3 clinical trial in Alström syndrome, that we anticipate we can initiate in 2018. We believe that the combined Bardet-Biedl syndrome and Alström syndrome Phase 3 pivotal trial may be somewhat different in design that those for POMC and LepR deficiency obesity, respectively, most likely due to the larger available patient population for inclusion in a clinical study. There may be other changes as well, as our feedback from the FDA is preliminary, and we have not yet consulted with the European regulatory agencies. We have also initiated Phase 2 clinical trials for POMC and other MC4 pathway heterozygous deficiency obesities, and POMC epigenetic disorders. We anticipate that the Phase 2 clinical trials in these indications may be more complex than those for which we have achieved proof of concept.

Successful completion of such Phase 3 clinical trials is a prerequisite to submitting an NDA to the FDA, a marketing authorization application to the EMA, and other applications for marketing authorization to equivalent competent authorities in foreign jurisdictions, and consequently, the ultimate approval and commercial marketing of setmelanotide. While we believe that a transition from proof of concept to pivotal trials may be more straight-forward for Alström syndrome, it is likely that Phase 2 clinical trials will be longer and more complex for POMC heterozygous deficiency obesity and POMC epigenetic disorders, due to the greater variety of clinical presentation in those conditions.

We do not know whether our planned additional Phase 2 or Phase 3 clinical trials will begin or whether any of our clinical trials will be completed on schedule, if at all, as the commencement and successful completion of clinical trials can be delayed or prevented for a number of reasons, including but not limited to:

- the FDA or other equivalent competent authorities in foreign jurisdictions may deny permission to proceed with our planned Phase 3 clinical trials or any other clinical trials we may initiate, or may place a clinical trial on hold;
- delays in filing or receiving approvals or additional IND that may be required;
- negative results from our ongoing and planned preclinical studies, or the FDA or other equivalent competent authorities in foreign jurisdictions requiring additional preclinical studies;
- delays in commencing additional necessary preclinical studies, including carcinogenicity and juvenile toxicology studies;
- delays in reaching or failing to reach agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- since many already diagnosed patients are at academic sites, delays in conducting clinical trials at academic sites due to the particular challenges and delays typically associated with those sites, as well as the lack of alternatives to these sites which have already-diagnosed patients;

- inadequate quantity or quality of setmelanotide or other materials necessary to conduct clinical trials, including delays in the manufacturing of sufficient supply of finished drug product;

- difficulties in obtaining Institutional Review Board, or IRB, and/or ethics committee approval to conduct a clinical trial at a prospective site or sites;

- challenges in recruiting and enrolling patients to participate in clinical trials, including the size and nature of the patient population, the proximity of patients to clinical trial sites, eligibility criteria for the clinical trial, the nature of the clinical trial protocol, the availability of approved effective treatments for the relevant disease and competition from other clinical trial programs for similar indications;

- severe or unexpected drug-related side effects experienced by patients in a clinical trial, including side effects previously identified in our completed clinical trials;

- delays in identifying and recruiting patients with any of the genetic causes of obesity in indications that we are targeting;

- disagreement by the FDA, other regulatory agencies or the equivalent competent authorities in foreign jurisdictions with our clinical trial designs, which may in turn cause delays in initiating our clinical trials, or may lead to rejection of our interpretation of data from clinical trials or to changes in the requirements for approval even after it has reviewed and commented on the design for our clinical trials;

- the requirement to have a placebo controlled study even though the FDA and EMA did not impose one for POMC deficiency obesity, as we cannot be certain that this will be true for other indications or that the FDA or EMA, an advisory committee or the equivalent competent authorities in foreign jurisdictions will not change its guidance, as it has done so in the past for other open control trials;

- uncertainty related to the length of placebo-controlled intervals in clinical trials;

- the need to perform non-inferiority trials, which can be larger, longer and more costly, if treatment is approved for similar indications;

- potential delays in the enrollment for our clinical trials of Bardet-Biedl syndrome and Alström syndrome due to the fact that we have not yet completed our discussions with the FDA regarding clinical trials for these indications, do not know if the FDA will disagree with our proposed Phase 3 clinical trial design;

- potential difficulties in defining the indication for Bardet-Biedl syndrome, as there may be discrepancies between the syndromic, or clinical definition of the syndrome, and the genetic confirmation of the indication;

- lack of ability to predict which patients will have the most consistent responses to setmelanotide in the patients with rare genetic disorders of obesity that we are studying, as not all patients may show robust responses to treatment;

- POMC heterozygous deficiency may have additional challenges, including that the FDA the EMA, or the equivalent competent authorities in foreign jurisdictions may require that we show that setmelanotide works better in these patients than in the genetically normal population; other challenges associated with these patients may include additional delays in initiating clinical trials for this indication due to uncertainty about the subset of these patients who will respond effectively to setmelanotide and the lack of discussion for this indication with the FDA;

- reports from preclinical or clinical testing of other weight loss therapies may raise safety or efficacy concerns;

- difficulties retaining patients who have enrolled in a clinical trial but may be prone to withdraw due to rigors of the clinical trial, lack of efficacy, side-effects, personal issues or loss of interest; and

- lack of a complete understanding of the absorption, distribution, metabolism and excretion of setmelanotide, or an incomplete set of clinical pharmacology studies to support labeling.

Clinical trials may also be delayed or terminated as a result of ambiguous or negative interim results. In addition, a clinical trial may be suspended or terminated by us, the FDA or other equivalent competent authorities in foreign jurisdictions, the IRBs or ethics committees at the sites where the IRBs or the ethics committees are overseeing a clinical trial, a data and safety monitoring board, or DSMB, or Safety Monitoring Committee, or SMC, overseeing the clinical trial at issue or other equivalent competent authorities due to a number of factors, including, among others:

- failure to conduct the clinical trial in accordance with regulatory requirements or our clinical trial protocols;

- inspection of the clinical trial operations or trial sites by the FDA or other equivalent competent authorities that reveals deficiencies or violations that require us to undertake corrective action, including the imposition of a clinical hold;

- unforeseen safety issues, adverse side effects or lack of effectiveness;

- changes in government regulations or administrative actions;

- problems with clinical trial supply materials; and

- lack of adequate funding to continue the clinical trial.

Changes in regulatory requirements, FDA or EMA guidance or unanticipated events during our clinical trials of setmelanotide may occur, which may result in changes to clinical trial protocols, changes to instruments for measuring subjective systems or additional clinical trial requirements, which could result in increased costs to us and could delay our development timeline.

Changes in regulatory requirements, FDA guidance, guidance published by the EMA or the other competent authorities in foreign jurisdictions, or unanticipated events during our clinical trials may force us to amend clinical trial protocols or the FDA, or the other competent authorities in foreign jurisdictions may impose additional clinical trial requirements. For instance, the FDA issued draft guidance on developing products for weight management in February 2007. In March 2012, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee met to discuss possible changes to how the FDA evaluates the cardiovascular safety of weight-management drugs, and the FDA may require additional studies to support registration. In addition, the FDA is considering broader applicability of requirements for cardiovascular outcomes trials, or CVOTs, presenting the possibility of cardiovascular risk pre-approval, including for obesity products. While our Phase 3 discussions with the FDA have not resulted in a requirement for any of these activities, any future requirement for these activities could result in additional clinical requirements for setmelanotide, increase our costs and delay approval of setmelanotide.

Amendments to our clinical trial protocols would require resubmission to the FDA and IRBs or other competent authorities and ethics committees in foreign jurisdictions for review and approval, which may adversely impact the cost, timing or successful completion of a clinical trial. If we experience delays completing, or if we terminate, any of our clinical trials, or if we are required to conduct additional clinical trials, the commercial prospects for setmelanotide may be harmed and our ability to generate product revenue will be delayed.

In addition, as part of commencing our Phase 3 clinical trial for setmelanotide in POMC deficiency obesity, we sought FDA concurrence with, and received substantial input on, the use of Patient Reported Outcome, or PRO, and Observer Reported Outcome, or ORO, questionnaires for measuring subjective endpoints for changes in hunger and/or food-seeking behavior and compulsions. We believe we can apply the same guidance to our future pivotal trials in other indications. A PRO is a measurement based on a report that comes from the patient about the status of a patient's health condition, without amendment or interpretation of the patient's response by a clinician or anyone else. An ORO is a measurement based on an observation by someone other than the patient or a health professional, such as a parent, spouse or other non-clinical caregiver who is in a position to regularly observe and report on a specific aspect of the patient's health. In our Phase 3 clinical trials for setmelanotide, based on the FDA feedback, we plan to measure the ability of setmelanotide to mitigate hunger and/or hyperphagia, the overriding physiological drive to eat, through PRO and ORO questionnaires. The questionnaires are designed to elicit feedback from patients on how well setmelanotide decreases their hunger, and from their family members or caregivers on the effect of setmelanotide on the patients' food seeking behavior.

To our knowledge, no sponsor of an approved drug has yet used PRO or ORO questionnaires to generate data on hyperphagia or hunger mitigating endpoints. Because we may be relying on clinical endpoints that have not previously been the subject of prior FDA approvals, there is a risk that the FDA or other equivalent competent authorities in foreign jurisdictions may not consider the endpoints to provide evidence of clinically meaningful results or that results may be difficult for the FDA to interpret, in particular for the pediatric age group. If we experience delays in our ongoing validation of our PRO or ORO questionnaires, or do not receive agreement with those proposed questionnaires based on the conceptual framework, content reliability, other measures of validity, or their ability to detect changes in hyperphagia or hunger, or we experience difficulties in the methods of statistical analysis for hunger and hyperphagia, we may experience delays in our trials or in product approval as well as be unable to reference data on hyperphagia or hunger in our product labeling. Finally, our Phase 3 clinical trials will be assessing hunger using multiple methods, some of which were previously used in Phase 2, but some of which were initiated in Phase 3 trials and for which little data is available. Hence it is possible that the effects on hunger seen in Phase 2 trials may differ with some of the new methodologies for assessing hunger being used in Phase 3 trials, or may not support language in the proposed product labeling.

Setmelanotide may cause undesirable side effects that could delay or prevent regulatory approval, limit the commercial profile of an approved labeling, or result in significant negative consequences following marketing approval, if any.

First generation MC4R agonists were predominantly small molecules that failed in clinical trials due to significant safety issues, particularly increases in blood pressure, and had limited efficacy. Undesirable side effects caused by setmelanotide could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive labeling or the delay or denial of regulatory approval by the FDA or other equivalent competent authorities in foreign jurisdictions.

Setmelanotide is an MC4R agonist. Potential side effects of MC4R agonism, which have been noted either with setmelanotide or with other MC4R agonists in clinical trials and preclinical studies, may include:

- adverse effects on cardiovascular parameters, such as increases in heart rate and blood pressure;
- erections in males and similar effects in women, such as sexual arousal, clitoral swelling and hypersensitivity;
- nausea and vomiting;
- reduced appetite;
- effects on mood, depression, anxiety and other psychiatric manifestations; and
- other effects, specifically adverse events noted at somewhat greater rates numerically for setmelanotide compared to placebo across the clinical program, which include fatigue and related

symptoms, diarrhea, arthralgia, back pain and headache, though most investigators reported these effects to be unrelated to setmelanotide.

Injection site reactions have been seen in subcutaneous, or SC, injections with setmelanotide. In addition, setmelanotide has likely off-target effects on the closely-related MC1 receptor, which mediates tanning in response to sun exposure. Other MC1 receptor mediated effects include darkening of skin blemishes, such as freckles and moles, and hair color change. The cosmetic effects are not tolerated by all patients, as a small number of patients have withdrawn from treatment due to tanning. These effects have generally been reversible in clinical trials, but it is still unknown if they will be reversible with long-term exposure. The MC1 receptor mediated effects may also carry risks. The long-term impact of MC1 receptor activation has not been tested in clinical trials, and could potentially include increases in skin cancer, excess biopsy procedures and cosmetic blemishes. These skin changes may also result in unblinding, which could make interpretation of clinical trial results more complex and possibly subject to bias.

The safety data we have disclosed to date represents our interpretation of the data at the time of disclosure and they are subject to our further review and analysis. There has been only a single serious adverse event possibly attributed to setmelanotide in our clinical trials. In our Phase 2 clinical trial with once daily SC injection, one patient was hospitalized for unusual chest pain, but no evidence of any serious respiratory or cardiac cause was found after careful evaluation, and the event was attributed to musculoskeletal pain. There were no treatment related changes in physical examination, except as noted below, and few, if any, clinically relevant changes in electrocardiograms, laboratory data and/or anti-drug antibodies. Overall, there have been ten other serious adverse events in the full development program, in addition to the serious adverse event described above: seven others on setmelanotide, mostly from open label trials, including left arm numbness, influenza immunization reaction, pancreatitis secondary to pre-existing gallstones, pneumonia, hypoglycemia due to acute adrenal insufficiency, due to non-compliance with hydrocortisone regimen, a depressive episode with elective admission to a psychiatry ward in a patient with history of depression and who continued on treatment, and rotavirus-related gastroenteritis. There were also three serious adverse events during treatment with placebo, consisting of biliary dyskinesia, severe groin strain, and pelvic inflammatory disease. None of these serious adverse events was considered related to setmelanotide treatment.

We are also initiating trials of setmelanotide in potential new indications that include patients who might have more serious underlying conditions, such as Alström syndrome, lipodystrophy and other indications. It is possible that the underlying conditions in these patients, such as congestive heart failure, pancreatitis, and potentially other conditions may confound the understanding of the safety profile of setmelanotide.

In addition, our interpretation of the safety data from our clinical trials is contingent upon the review and ultimate approval of the FDA, other regulatory authorities or other equivalent competent authorities in foreign jurisdictions. The FDA or other equivalent competent authorities in foreign jurisdictions may not agree with our methods of analysis or our interpretation of the results. In addition, the long-term effects of setmelanotide have only been tested in a limited number of patients.

Further, if setmelanotide receives marketing approval and we or others identify undesirable side effects caused by the product, or any other similar product, before or after the approval, a number of potentially significant negative consequences could result, including:

- regulatory authorities may request that we withdraw the product from the market or may limit their approval of the product through labeling or other means;
- regulatory authorities may require the addition of labeling statements, such as a "boxed" warning or a contraindication;
- the FDA and other equivalent competent authorities in foreign jurisdictions may require the addition of a Risk Evaluation and Mitigation Strategy, or REMS, or other specific obligations as a

condition for marketing authorization due to the need to limit treatment to rare patient populations, or to safety concerns;

- we may be required to change the way the product is distributed or administered, conduct additional clinical trials or change the labeling of the product;
- we may decide to remove the product from the marketplace;
- we could be sued and held liable for injury caused to individuals exposed to or taking the product; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of setmelanotide and could substantially increase the costs of commercializing setmelanotide and significantly impact our ability to successfully commercialize setmelanotide and generate revenues.

Although we have been granted orphan drug designation for setmelanotide in treating POMC deficiency obesity and LepR deficiency obesity, we may be unable to obtain orphan drug designation for other uses or to obtain exclusivity in any use. Even with exclusivity, competitors may obtain approval for different drugs that treat the same indications as setmelanotide.

The FDA may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, or the Orphan Drug Act, the FDA may designate a product candidate as an orphan drug if it is intended to treat a rare disease or condition, which is defined under the Federal Food, Drug and Cosmetic Act, or FDCA, as having a patient population of fewer than 200,000 individuals in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States.

Generally, if a product candidate with an orphan drug designation receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of seven years of marketing exclusivity, which precludes the FDA from approving another marketing application for a product that constitutes the same drug treating the same indication for that marketing exclusivity period, except in limited circumstances.

The exclusivity period in the United States can be extended by six months if the NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. Even under these circumstances, we may not be granted pediatric approval from the FDA for these indications. Orphan drug exclusivity may be revoked if the FDA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition. Other potential benefits of orphan drug designation and/or approval of a designated drug include eligibility for: exemption from certain prescription drug user fees, tax credits for certain qualified clinical testing expenses, and waivers from the pediatric assessment requirements of the Pediatric Research Equity Act, or PREA.

Although we have been granted orphan drug designation for setmelanotide in treating POMC deficiency obesity and LepR deficiency obesity, if we request orphan drug designation for setmelanotide for other uses, there can be no assurance that the FDA will grant such designation. For example, if the population of patients who would be appropriate candidates for a drug is 200,000 or more individuals, the drug may not qualify for orphan drug designation, even if the population for which the sponsor seeks approval is lower than 200,000. Additionally, the designation of setmelanotide as an orphan drug does not guarantee that the FDA will accelerate regulatory review of, or ultimately approve, setmelanotide.

Even if we obtain orphan drug exclusivity for setmelanotide, that exclusivity may not effectively protect setmelanotide from competition because different drugs can be approved for the same condition.

In the United States, even after an orphan drug is approved, the FDA may subsequently approve another drug for the same condition if the FDA concludes that the latter drug is not the same drug or is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care.

On August 3, 2017, Congress passed the FDA Reauthorization Act of 2017, or the FDARA. FDARA, among other things, codified the FDA's pre-existing regulatory interpretation, to require that a drug sponsor demonstrate the clinical superiority of an orphan drug that is otherwise the same as a previously approved drug for the same rare disease in order to receive orphan drug exclusivity. The new legislation reverses prior precedent holding that the Orphan Drug Act unambiguously requires that the FDA recognize the orphan exclusivity period regardless of a showing of clinical superiority. The FDA may further reevaluate the Orphan Drug Act and its regulations and policies. We do not know if, when, or how the FDA may change the orphan drug regulations and policies in the future, and it is uncertain how any changes might affect our business. Depending on what changes the FDA may make to its orphan drug regulations and policies, our business could be adversely impacted.

Although we have obtained Breakthrough Therapy designation for setmelanotide for the treatment of obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway, which includes POMC deficiency obesity, LepR deficiency obesity, Bardet-Biedl syndrome and Alström syndrome, the FDA may rescind the Breakthrough Therapy Designation and we may be unable to obtain Breakthrough Therapy designation for other uses. In addition, Breakthrough Therapy designation by the FDA may not lead to a faster development, regulatory review or approval process, and it does not increase the likelihood that setmelanotide will receive marketing approval in the United States.

Under the Food and Drug Administration Safety and Innovation Act, or FDASIA, the FDA is authorized to give certain products "Breakthrough Therapy designation." A Breakthrough Therapy product candidate is defined as a product candidate that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that such product candidate may demonstrate substantial improvement on one or more clinically significant endpoints over existing therapies. The FDA will seek to ensure the sponsor of Breakthrough Therapy product candidate receives intensive guidance on an efficient drug development program, intensive involvement of senior managers and experienced staff on a proactive, collaborative and cross-disciplinary review and a rolling review process whereby the FDA may consider reviewing portions of an NDA before the sponsor submits the complete application. Product candidates designated as breakthrough therapies by the FDA may be eligible for other expedited programs, such as priority review, if supported by clinical data.

Designation as Breakthrough Therapy is within the discretion of the FDA. Accordingly, even if we believe setmelanotide meets the criteria for designation as Breakthrough Therapy for other uses, the FDA may disagree. In any event, the receipt of Breakthrough Therapy designation for a product candidate, or acceptance for one or more of the FDA's other expedited programs, may not result in a faster development process, review or approval compared to products considered for approval under conventional FDA procedures and does not guarantee ultimate approval by the FDA. Additionally, the FDA may later decide that the product candidate no longer meets the conditions for designation and may withdraw designation at any time or decide that the time period for FDA review or approval will not be shortened.

We may not be able to translate the current formulations of setmelanotide for methods of delivery that would be acceptable to the FDA or other equivalent competent authorities in foreign jurisdictions or commercially successful.

Setmelanotide is currently administered by SC injection using small insulin-type needles. SC injection is generally less well-received by patients than other methods of administration, such as oral administration. Considerable additional resources and efforts, including potential studies, may be necessary in order to translate the current formulations of setmelanotide into forms that will be well-received by patients.

We have entered into a license agreement with Camurus AB, or Camurus, for the use of Camurus' drug delivery technology, FluidCrystal, to formulate setmelanotide. This formulation, if successfully developed for setmelanotide, will be delivered subcutaneously, similar to our current formulation, except that we anticipate it will be injected once weekly. The initial Phase 1 pharmacokinetic data from healthy obese volunteers supports once-weekly dosing, but has only been administered for short durations. It is possible that the tolerability profile and/or pharmacokinetics in patients will not be similar to that of healthy obese volunteers, making development of this product more complex. In addition, we have not consulted with regulatory agencies about the path for approval of the once-weekly formulation, and, accordingly, we cannot estimate the time, cost, and probability of success for approval. The Camurus formulations have also not been approved for any product at this time, which further complicates our understanding for the path to approval. While we plan to utilize the current formulation, or to develop new and useful formulations and delivery technology for setmelanotide, we cannot estimate the probability of success, nor the resources and time needed to succeed. If we are unable to utilize this formulation, or to develop new formulations, setmelanotide may not achieve significant market acceptance and our business, financial condition and results of operations may be materially harmed.

Our approach to treating patients with MC4 pathway deficiencies requires the identification of patients with unique genetic subtypes, for example, POMC genetic deficiency. The FDA or other equivalent competent authorities in foreign jurisdictions could require the approval or CE mark of an in vitro companion diagnostic device to ensure appropriate selection of patients as a condition of approving setmelanotide. The development and approval or CE mark of an in vitro companion diagnostic device would require substantial financial resources and could delay regulatory approval of setmelanotide.

We intend to focus our development of setmelanotide as a treatment for obesity caused by certain genetic deficiencies affecting the MC4 pathway. In order to assist in identifying this subset of patients, we employ a genetic diagnostic test, which is a test or measurement that evaluates the presence of genetic variants in a patient. The FDA has previously advised that for our clinical trial of setmelanotide to treat POMC deficiency obesity, it will be sufficient to use genetic diagnostic testing known as Sanger bi-directional nucleotide sequencing, as long as that testing is performed by laboratories meeting the standards of the Clinical Laboratory Improvement Amendments, or CLIA, for Laboratory Developed Tests, or LDTs. Currently the Centers for Medicare and Medicaid Services, or CMS, regulates LDTs and the laboratories that develop them, and enforces CLIA. CMS evaluates whether there is clinical utility for each specific test, and also performs postmarket oversight of laboratory operational processes. CMS coverage determinations of clinical utility measure the ability of the test to impact clinically meaningful health outcomes, such as mortality or morbidity, through the adoption of efficacious treatments. CMS's oversight through the CLIA program is designed to confirm that a lab assesses analytical validity, but does not confirm whether it had results from an analytical validity assessment that were sufficient to support the claimed intended use of the test. The FDA has issued guidance indicating, however, that in the future it intends to assert jurisdiction over LDTs and to increase regulatory requirements for LDTs. If the FDA does so, the burdens and costs of using LDTs to select patients for setmelanotide could increase, the availability of those LDTs could be negatively affected, and our development program for setmelanotide could be delayed, which in turn could delay or impair our ability to proceed to commercialization.

Although the FDA had previously advised us that an LDT is sufficient for identifying patients in our clinical trials, the agency also previously indicated that approval of an *in vitro* companion diagnostic device may be necessary should clinical results reveal that genetic testing is needed for the safe use of setmelanotide, such as to avoid significant toxicities in certain patients or because the drug might provide only marginal benefits except in a very clearly defined eligible population. More recent communications from the FDA have increased the potential for a need for a companion diagnostic device. *In vitro* companion diagnostic devices provide information that is essential for the safe and effective use of a corresponding therapeutic product. These companion diagnostic devices may be co-developed with a device manufacturer or with a laboratory, and generally require FDA approval as well.

Should the FDA or other equivalent competent authorities in foreign jurisdictions require the use of a companion diagnostic device, we may face significant delays or obstacles in obtaining approval of an NDA, or of comparable foreign marketing authorization for setmelanotide as the FDA or other equivalent competent authorities in foreign jurisdictions may take the position that a companion diagnostic device is required prior to granting approval of setmelanotide. In addition, we may be dependent on the sustained cooperation and effort of third-party collaborators with whom we may partner in the future to develop *in vitro* companion diagnostic devices. We and our potential future collaborators may encounter difficulties in developing such tests, including issues relating to the selectivity and/or specificity of the diagnostic, analytical validation, reproducibility or clinical validation. Any delay or failure by us or our potential future collaborators to develop or obtain regulatory clearance or approval of, or to CE mark, such tests, if necessary, could delay or prevent approval of setmelanotide.

If the FDA deems setmelanotide to require an *in vitro* companion diagnostic device to accurately identify the patients who belong to the target subset, the FDA will require product labeling that limits use to only those patients who express the genetic variants identified by the device. Moreover, even if setmelanotide and an *in vitro* companion diagnostic device are approved together, the device itself may be subject to reimbursement limitations that could limit access to treatment and therefore adversely affect our business and financial results.

We also are discussing with the FDA the specific mutations, or variants, that will define each indication for which we intend to seek approval. Our efforts have focused on loss-of-function variants that effectively inactivate the genes in the MC4 pathway, and we have proposed rules to define these variants for approval, and which can be used to categorize new variants as they are identified. The FDA has asked us to consider an alternative approach for categorizing and validating these variants that has been used for other diagnostics, and we are likely to agree.

In addition, we intend to apply genetic tests to address goals beyond seeking FDA approval of setmelanotide, including supporting efforts to explore and expand the diagnosis of patients with genetic causes of obesity, and to assist in building awareness of these illnesses. As such, we may develop or work with partners to develop additional genetic tests in the area of genetic obesity, including panels that may study a larger number of genes. There are many factors that might influence the success of these efforts, which could be impactful on our commercial efforts, including the cost, analytical methods, and the ability to provide clinical and diagnostic information to patients and doctors.

We have only one product candidate in clinical development and we may not be successful in any future efforts to identify and develop additional product candidates.

We have only one product candidate in clinical development and may seek to identify and develop additional product candidates for clinical development, both within and outside of our current area of expertise. If so, the success of our business may depend primarily on our ability to identify, develop and commercialize these products. Research programs to identify new product candidates require substantial technical, financial and human resources. We may fail to identify other potential product candidates for clinical development for a number of reasons. Our research methodology may be unsuccessful in identifying potential product candidates or our potential product candidates may be shown to have harmful side effects or may have other characteristics that may make the products unmarketable or unlikely to receive marketing approval. We may focus our efforts and resources on potential programs or product candidates that ultimately prove to be unsuccessful. In addition, any such efforts could adversely impact our continued development and commercialization of setmelanotide.

If any of these events occur, we may be forced to abandon some or all of our development efforts for a program or programs, which would have a material adverse effect on our business and could potentially cause us to cease operations.

Prader-Willi syndrome, or PWS, is a complex disease, and companies have had difficulties in developing new therapies for PWS.

Although we have been granted orphan drug designation for setmelanotide in treating PWS, we are not moving directly towards a Phase 3 trial in PWS at this time, but instead will be continuing to evaluate setmelanotide in another Phase 2 trial. We do not know the probability that we will be able to succeed in this additional Phase 2 trial and/or to proceed to Phase 3 and/or approval, even when these efforts are completed. In addition, the experience by others suggests that PWS patients are high risk for adverse experiences and for this, and many other reasons, clinical trials in that population are extremely challenging. It may be both difficult to determine if adverse effects in this population are due to the disease, setmelanotide or some combination of both. PWS is a complex multigenic disease, and the hypothesis that PWS is an upstream MC4 pathway disorder is supported primarily on the role of only one of those genes, MAGEL2, in animal models of obesity. Our results may support that PWS is not an upstream MC4 pathway disorder. Alternatively, other design factors may have influenced the outcome of this trial, and we will be reassessing in 2018 the possibility of future Phase 2 trials in PWS that address the following potential factors: duration of treatment, younger age of population, improved setmelanotide pharmacokinetics, consideration of higher doses, and operational limitations of the completed Phase 2 trial. There can be no assurances that some of the factors that affected the results of the PWS trials will not also adversely impact the results of our trials for other indications.

In addition, we have begun a program for a new mechanism that may have therapeutic effects in PWS, but this program is in preclinical development, and our candidate, RM-853, may not succeed in completing the pre-IND studies needed to proceed to clinical trials, or may fail in early Phase 1 studies due to unfavorable safety, pharmacokinetics or for other reasons. The hypothesis supporting the therapeutic effects of this mechanism is also based on limited clinical and preclinical information, and even if RM-853 were to progress to a Phase 2 proof of concept study, it is unclear if there will be safety and efficacy to support proceeding further in development.

Risks Related to the Commercialization of Setmelanotide

Even if approved, reimbursement policies could limit our ability to sell setmelanotide.

Market acceptance and sales of setmelanotide will depend on reimbursement policies and may be affected by healthcare reform measures. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels for those medications. Cost containment is a primary concern in the U.S. healthcare industry and in foreign jurisdictions. Government authorities and these third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. We cannot be sure that reimbursement will be available for setmelanotide and, if reimbursement is available, the level of such reimbursement. Reimbursement may impact the demand for, or the price of setmelanotide. If reimbursement is not available or is available only at limited levels, we may not be able to successfully commercialize setmelanotide.

In some foreign countries, particularly in Canada and in the EU member states, the pricing of prescription pharmaceuticals is subject to strict governmental control. In these countries, pricing negotiations with governmental authorities can take six to 12 months or longer after the receipt of regulatory approval and product launch. To obtain favorable reimbursement for the indications sought or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of setmelanotide with other available therapies. If reimbursement for setmelanotide is unavailable in any country in which we seek reimbursement, if it is limited in scope or amount, if it is conditioned upon our completion of additional clinical trials or if pricing is set at unsatisfactory levels, our operating results could be materially adversely affected.

In the EU, in particular, each EU member state can restrict the range of medicinal products for which its national health insurance system provides reimbursement and can control the prices of medicinal products for human use marketed in its territory. As a result, following receipt of marketing authorization in an EU member state, through any application route, an applicant is required to engage in pricing discussions and negotiations with the competent pricing authority in the individual EU member states. Some EU member states operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed upon. Other EU member states approve a specific price for the medicinal product or may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. The downward pressure on healthcare costs in general, particularly prescription drugs, has become more intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, we may face competition for setmelanotide from lower priced products in foreign countries that have placed price controls on pharmaceutical products.

Health Technology Assessment, or HTA, of medicinal products, however, is becoming an increasingly common part of the pricing and reimbursement procedures in some EU member states, including the United Kingdom, France, Germany, Ireland, Italy, Spain, and Sweden. HTA is the procedure according to which the assessment of the public health impact, therapeutic impact and the economic and societal impact of use of a given medicinal product in the national healthcare systems of the individual country is conducted. HTA generally focuses on the clinical efficacy and effectiveness, safety, cost, and cost-effectiveness of individual medicinal products as well as their potential implications for the healthcare system. Those elements of medicinal products are compared with other treatment options available on the market. The outcome of HTA regarding specific medicinal products will often influence the pricing and reimbursement status granted to these medicinal products by the competent authorities of individual EU member states. The extent to which pricing and reimbursement decisions are influenced by the HTA of the specific medicinal product varies between EU member states. In addition, pursuant to Directive 2011/24/EU on the application of patients' rights in cross-border healthcare, a voluntary network of national authorities or bodies responsible for HTA in the individual EU member states was established. The purpose of the network is to facilitate and support the exchange of scientific information concerning HTAs. This may lead to harmonization of the criteria taken into account in the conduct of HTAs between EU member states and in pricing and reimbursement decisions and may negatively affect price in at least some EU member states.

If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell setmelanotide, if approved, we may not be able to generate any revenue.

We do not currently have infrastructure in place for the sale, marketing or distribution of pharmaceutical products. In order to market setmelanotide, if approved by the FDA or other equivalent competent authorities in foreign jurisdictions, we must build our sales, marketing, managerial and other non-technical capabilities or make arrangements with third parties to perform these services. If we are unable to establish adequate sales, marketing and distribution capabilities, whether independently or with third parties, or if we are unable to do so on commercially reasonable terms, our business, results of operations, financial condition and prospects would be materially adversely affected.

Even if we receive marketing approval for setmelanotide in the United States, we may never receive regulatory approval to market setmelanotide outside of the United States.

We intend to pursue marketing approval for setmelanotide in the EU and in other countries worldwide. In order to market any product outside of the United States, we must establish and comply with the numerous and varying safety, efficacy and other regulatory requirements of other countries. Approval procedures vary among countries and can involve additional setmelanotide testing and additional administrative review periods. The time required to obtain approvals in other countries might differ from that required to obtain FDA approval. The marketing approval processes in other countries may implicate all of the risks detailed above regarding FDA approval in the United States as well as other risks. In particular, in many countries outside of the United States, products must receive pricing and reimbursement approval before the product can be commercialized. Obtaining this approval can result in substantial delays in bringing products to market in such countries. Marketing approval in one country does not ensure marketing approval in another, but a failure or delay in obtaining marketing approval in one country may have a negative effect on the regulatory process or commercial activities in others. Failure to obtain marketing approval in other countries or any delay or other setback in obtaining such approval would impair our ability to market setmelanotide in such foreign markets. Any such impairment would reduce the size of our potential market share and could have a material adverse impact on our business, results of operations and prospects.

Even if we receive marketing approval for setmelanotide, we may not achieve market acceptance, which would limit the revenue that we generate from the sale of setmelanotide.

The commercial success of setmelanotide, if approved by the FDA or other equivalent competent authorities in foreign jurisdictions, will also depend upon the awareness and acceptance of setmelanotide within the medical community, including physicians, patients and third-party payors. If setmelanotide is approved but does not achieve an adequate level of acceptance by patients, physicians and third-party payors, we may not generate sufficient revenue to become or remain profitable. Before granting reimbursement approval, third-party payors may require us to demonstrate that, in addition to treating obesity caused by certain genetic deficiencies affecting the MC4 pathway, setmelanotide also provides incremental health benefits to patients. Our efforts to educate the medical community and third-party payors about the benefits of setmelanotide may require significant resources and may never be successful. All of these challenges may impact our ability to ever successfully market and sell setmelanotide.

Market acceptance of setmelanotide, if approved, will depend on a number of factors, including, among others:

- the ability of setmelanotide to treat obesity caused by certain genetic deficiencies affecting the MC4 pathway and, if required by any competent authority in connection with the approval for these indications, to provide patients with incremental health benefits, as compared with other available treatments, therapies, devices or surgeries;
- the relative convenience and ease of SC injections as the necessary method of administration of setmelanotide, including as compared with other treatments for obese patients;
- the prevalence and severity of any adverse side effects associated with setmelanotide;
- limitations or warnings contained in the labeling approved, as well as the existence of a REMS, for setmelanotide by the FDA or the specific obligations imposed as a condition for marketing authorization imposed by other equivalent competent authorities in foreign jurisdictions, particularly by the European Commission;
- availability of alternative treatments, including a number of obesity therapies already approved or expected to be commercially launched in the near future;
- the size of the target patient population, and the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the ability of setmelanotide to treat the maximum range of pediatric patients, and any limitations on its indications for use, such as if the labeling limits the approved population to patients ages 12 and above;
- the strength of marketing and distribution support and timing of market introduction of competitive products;

- publicity concerning setmelanotide or competing products and treatments;
- pricing and cost effectiveness;
- the effectiveness of our sales and marketing strategies;
- our ability to increase awareness of setmelanotide through marketing efforts;
- our ability to obtain sufficient third-party coverage or reimbursement;
- the willingness of patients to pay out-of-pocket in the absence of third-party coverage; and
- the likelihood that the FDA or other equivalent competent authorities in foreign jurisdictions may require development of a REMS as a condition of approval or post-approval, may not agree with our proposed REMS or may impose additional requirements that limit the promotion, advertising, distribution or sales of setmelanotide.

Our industry is intensely competitive. If we are not able to compete effectively against current and future competitors, we may not be able to generate revenue from the sale of setmelanotide, our business will not grow and our financial condition and operations will suffer.

The biotechnology and pharmaceutical industries are intensely competitive and subject to rapid and significant technological change. We have competitors in a number of jurisdictions, many of which have substantially greater name recognition, commercial infrastructures and financial, technical and personnel resources than we have. Established competitors may invest heavily to quickly discover and develop compounds that could make setmelanotide obsolete or uneconomical. Any new product that competes with an approved product may need to demonstrate compelling advantages in efficacy, convenience, tolerability and safety to be commercially successful. Other competitive factors, including generic competition, could force us to lower prices or could result in reduced sales. In addition, new products developed by others could emerge as competitors to setmelanotide. If we are not able to compete effectively against our current and future competitors, our business will not grow and our financial condition and operations will suffer.

Currently, there are no approved or effective current treatments for regulating hunger and hyperphagia related behaviors of patients with POMC deficiency obesity, LepR deficiency obesity, Bardet-Biedl syndrome, Alström syndrome, POMC heterozygous deficiency obesity, or POMC epigenetic disorders. Bariatric surgery is not a treatment option for these genetic disorders of obesity because the severe obesity and hyperphagia associated with these disorders are considered to be risk factors for bariatric surgery. While we are unaware of any competitive products in development for the obesity and hyperphagia caused by upstream MC4 pathway deficiencies specifically, new competitors may emerge which could limit our business opportunity in the future.

We face potential product liability exposure, and, if claims are brought against us, we may incur substantial liability.

The use of setmelanotide in clinical trials and the sale of setmelanotide, if approved, exposes us to the risk of product liability claims. Product liability claims might be brought against us by patients, healthcare providers or others selling or otherwise coming into contact with setmelanotide. For example, we may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design or a failure to warn of dangers inherent in the product, including as a result of interactions with alcohol or other drugs, negligence, strict liability and a breach of warranties. Claims could also be asserted under state consumer protection laws and any equivalent laws in foreign countries. If we become subject to product liability claims and cannot successfully defend ourselves against them, we could incur substantial liabilities. In addition, regardless of merit or eventual outcome, product liability claims may result in, among other things:

- withdrawal of patients from our clinical trials;
- substantial monetary awards to patients or other claimants;
- decreased demand for setmelanotide or any future product candidates following marketing approval, if obtained;
- damage to our reputation and exposure to adverse publicity;
- litigation costs;
- distraction of management's attention from our primary business;
- loss of revenue; and
- the inability to successfully commercialize setmelanotide or any future product candidates, if approved.

We maintain product liability insurance coverage for our clinical trials with a $10.0 million annual aggregate coverage limit. Our insurance coverage may be insufficient to reimburse us for any expenses or losses we may suffer. Moreover, in the future, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses, including if insurance coverage becomes increasingly expensive. If and when we obtain marketing approval for setmelanotide, we intend to expand our insurance coverage to include the sale of commercial products. However, we may not be able to obtain this product liability insurance on commercially reasonable terms. Large judgments have been awarded in class action lawsuits based on drugs that had unanticipated side effects. The cost of any product liability litigation or other proceedings, even if resolved in our favor, could be substantial, particularly in light of the size of our business and financial resources. A product liability claim or series of claims brought against us could cause our stock price to decline and, if we are unsuccessful in defending such a claim or claims and the resulting judgments exceed our insurance coverage, our financial condition, business and prospects could be materially adversely affected.

Risks Related to Our Dependence on Third Parties

We rely, and expect that we will continue to rely, on third parties to conduct clinical trials for setmelanotide. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approval for or commercialize setmelanotide and our business could be substantially harmed.

We enter into agreements with third-party CROs to provide monitors for and to manage data for our ongoing clinical trials. We rely heavily on these parties for the execution of clinical trials for setmelanotide and control only certain aspects of their activities. As a result, we have less direct control over the conduct, timing and completion of these clinical trials and the management of data developed through the clinical trials than would be the case if we were relying entirely upon our own staff. Communicating with outside parties can also be challenging, potentially leading to mistakes as well as difficulties in coordinating activities. However, we remain responsible for the conduct of these trials and are subject to enforcement which may include civil and criminal liabilities for any violations of FDA rules and regulations and the comparable foreign regulatory provisions during the conduct of our clinical trials. Outside parties may:

- have staffing difficulties;
- fail to comply with contractual obligations;
- devote inadequate resources to our clinical trials;
- experience regulatory compliance issues;

- undergo changes in priorities or become financially distressed; or
- form more favorable relationships with other entities, some of which may be our competitors.

These factors may materially adversely affect the willingness or ability of third parties to conduct our clinical trials and may subject us to unexpected cost increases that are beyond our control. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards, and our reliance on CROs does not relieve us of our regulatory responsibilities. We and our CROs are required to comply with current Good Clinical Practices, or cGCPs, which are guidelines enforced by the FDA, the Competent Authorities of the EU member states and equivalent competent authorities in foreign jurisdictions for any products in clinical development. The FDA enforces these regulations and cGCP guidelines through periodic inspections of clinical trial sponsors, principal investigators, and trial sites, and IRBs. If we or our CROs fail to comply with applicable cGCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or other equivalent competent authorities in foreign jurisdictions may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that, upon inspection, the FDA will determine that any of our clinical trials comply with cGCPs. In addition, our clinical trials must be conducted with products produced under current Good Manufacturing Practices, or cGMPs. Our failure or the failure of our CROs to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process and could also subject us to enforcement action up to and including civil and criminal penalties.

If any of our relationships with these third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs. If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain are compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, any such clinical trials may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for, or successfully commercialize, setmelanotide. As a result, our financial results and the commercial prospects for setmelanotide in the subject indication would be harmed, our costs could increase and our ability to generate revenue could be delayed.

We rely completely on third-party suppliers to manufacture our clinical drug supplies of setmelanotide, and we intend to rely on third parties to produce commercial supplies of setmelanotide and preclinical, clinical and commercial supplies of any future product candidate.

We do not currently have, nor do we plan to acquire, the infrastructure or capability to internally manufacture our clinical drug supply of setmelanotide, or any future product candidates, for use in the conduct of our preclinical studies and clinical trials, and we lack the internal resources and the capability to manufacture any product candidate on a clinical or commercial scale. The facilities used by our contract manufacturing organizations, or CMOs, to manufacture the active pharmaceutical ingredient, or API, and final drug product must pass inspection by the FDA and other equivalent competent authorities in foreign jurisdictions pursuant to inspections that would be conducted after we submit our NDAs or relevant foreign regulatory submission to the other equivalent competent authorities in foreign jurisdictions. In addition, our clinical trials must be conducted with products produced under cGMP regulations.

Our failure or the failure of our CROs or CMOs to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process and could also subject us to enforcement action, including civil and criminal penalties. If we import any drugs or drug substances, we would be subject to FDA and U.S. Bureau of Customs and Border Patrol, or CBP, import regulation requirements. Such enforcement for our failure or our CROs or CMOs' failure to comply with these regulations could result in import delays, detention of products, and, depending on criteria such as the history of violative activities, the FDA could place a foreign firm or certain drug substances or products on Import Alert and require that all such drug substances or products be subject to detention without physical examination, or DWPE, which could significantly impact the global supply chain for setmelanotide. FDARA provides that prescription drug products, with the exception of those on the FDA's drug shortage list or properly imported by individuals, may not be imported for commercial use if they were manufactured in a foreign country, unless they have been approved or are otherwise authorized to be marketed in the United States and are labeled accordingly.

We currently contract with a third party for the manufacture of setmelanotide and intend to continue to do so in the future. We have entered into a process development and manufacturing services agreement with Corden Pharma Brussels S.A, or Corden, formerly Peptisyntha SA prior to its acquisition by Corden, under which Corden will provide certain process development and manufacturing services in connection with the manufacture of setmelanotide. We have also entered into a process development and manufacturing services agreement with Recipharm Monts S.A.S, or Recipharm, under which Recipharm will provide certain process development and manufacturing services in connection with the manufacture of setmelanotide. Under our agreements, we pay both Corden and Recipharm for services in accordance with the terms of mutually agreed upon work orders, which we, Corden and Recipharm may enter into from time to time. The agreement with Corden also provides that, subject to certain conditions, for a period following each product launch date, we will source from Corden a portion of our requirements for that product being sourced from non-affiliate third parties. We may need to engage additional third-party suppliers to manufacture our clinical drug supplies. In the future, if we approach commercialization of setmelanotide or any future product candidate, we will need to engage other third parties to assist in, among other things, labeling, packaging, distribution, post-approval safety reporting, and pharmacovigilance activities. We cannot be certain that we can engage third-party suppliers on terms as favorable as those that are currently in place.

We do not perform the manufacturing of any drug products, and are completely dependent on, our CMOs to comply with cGMPs for manufacture of both API and finished drug product. We recognize that we are ultimately responsible for ensuring that our drug substances and finished product are manufactured in accordance with cGMPs, and, therefore, the company's management practices and oversight, including routine auditing, are critical. If our CMOs cannot successfully manufacture material that conform to our specifications and the strict regulatory requirements of the FDA or other equivalent competent authorities in foreign jurisdictions, they may be subject to administrative and judicial enforcement for non-compliance and the drug products would be deemed misbranded or adulterated and prohibited from distribution into interstate commerce. Furthermore, all of our CMOs are engaged with other companies to supply and/or manufacture materials or products for such companies, which exposes our manufacturers to regulatory risks for the production of such materials and products. As a result, failure to satisfy the regulatory requirements for the production of those materials and products may affect the regulatory clearance of our CMOs' facilities generally. If the FDA or another equivalent competent foreign regulatory agency does not approve these facilities for the manufacture of setmelanotide or if it withdraws its approval in the future, we may need to find alternative manufacturing facilities, which would adversely impact our ability to develop, obtain regulatory approval for or market setmelanotide.

We are currently in the process of manufacturing finished drug product for use in our upcoming clinical trials. We believe we currently have a sufficient amount of finished setmelanotide, diluent and placebo to complete our planned clinical trials. However, these projections could change based on delays encountered with manufacturing activities, equipment scheduling and material lead times. Any such delays in the manufacturing of finished drug product could delay our planned clinical trials of setmelanotide, which could delay, prevent or limit our ability to generate revenue and continue our business.

We do not have long-term supply agreements in place with our contractors, and each batch of setmelanotide is individually contracted under a quality and supply agreement. If we engage new contractors, such contractors must be approved by the FDA and other equivalent competent authorities in foreign jurisdictions. We will need to submit information to the FDA and other equivalent competent authorities in foreign jurisdictions describing the manufacturing changes. If manufacturing changes occur post-approval, the FDA may have to approve these changes. We plan to continue to rely upon CMOs and, potentially, collaboration partners to manufacture commercial quantities of setmelanotide, if approved. Our current scale of manufacturing appears adequate to support all of our current needs for clinical trial supplies for setmelanotide. If setmelanotide is approved, we will need to identify CMOs or partners to produce setmelanotide on a larger scale.

Risks Related to Our Intellectual Property Rights

If we are unable to adequately protect our proprietary technology or maintain issued patents that are sufficient to protect setmelanotide, others could compete against us more directly, which would have a material adverse impact on our business, results of operations, financial condition and prospects.

Our commercial success will depend in part on our success in obtaining and maintaining issued patents and other intellectual property rights in the United States and elsewhere and protecting our proprietary technology. If we do not adequately protect our intellectual property and proprietary technology, competitors may be able to use our technologies and erode or negate any competitive advantage we may have, which could harm our business and ability to achieve profitability.

We cannot provide any assurances that any of our patents have, or that any of our pending patent applications that mature into issued patents will include, claims with a scope sufficient to protect setmelanotide. Other parties have developed technologies that may be related or competitive to our approach, and may have filed or may file patent applications and may have received or may receive patents that may overlap with our patent applications, either by claiming the same methods or formulations or by claiming subject matter that could dominate our patent position. The patent positions of biotechnology and pharmaceutical companies, including our patent position, involve complex legal and factual questions, and, therefore, the issuance, scope, validity and enforceability of any patent claims that we may obtain cannot be predicted with certainty.

Although an issued patent is presumed valid and enforceable, its issuance is not conclusive as to its validity or its enforceability and such patent may not provide us with adequate proprietary protection or competitive advantages against competitors with similar products. Patents, if issued, may be challenged, deemed unenforceable, invalidated or circumvented. U.S. patents and patent applications or the patents and patent application obtained or submitted pursuant to comparable foreign laws, may also be subject to interference proceedings, *ex parte* reexamination, *inter partes* review proceedings, post-grant review proceedings, supplemental examination and challenges in district court. Patents may be subjected to opposition or comparable proceedings lodged in various foreign, both national and regional, patent offices. These proceedings could result in either loss of the patent or denial of the patent application or loss or reduction in the scope of one or more of the claims of the patent or patent application. In addition, such proceedings may be costly. Thus, any patents that we may own or exclusively license may not provide any protection against competitors. Furthermore, an adverse decision in an interference proceeding can result in a third party receiving the patent right sought by us, which in turn could affect our ability to develop, market or otherwise commercialize setmelanotide.

Competitors may also be able to design around our patents. Other parties may develop and obtain patent protection for more effective technologies, designs or methods. The laws of some foreign countries do not protect our proprietary rights to the same extent as the laws of the United States, and we may encounter significant problems in protecting our proprietary rights in these countries. If these developments were to occur, they could have a material adverse effect on our sales.

In addition, proceedings to enforce or defend our patents could put our patents at risk of being invalidated, held unenforceable or interpreted narrowly. Such proceedings could also provoke third parties to assert claims against us, including that some or all of the claims in one or more of our patents are invalid or otherwise unenforceable. If any of our patents covering setmelanotide are invalidated or found unenforceable, our financial position and results of operations would be materially and adversely impacted. In addition, if a court found that valid, enforceable patents held by third parties covered setmelanotide, our financial position and results of operations would also be materially and adversely impacted.

The degree of future protection for our proprietary rights is uncertain, and we cannot ensure that:

- any of our patents, or any of our pending patent applications, if issued, will include claims having a scope sufficient to protect setmelanotide;
- any of our pending patent applications will issue as patents;
- we will be able to successfully commercialize setmelanotide, if approved, before our relevant patents expire;
- we were the first to make the inventions covered by each of our patents and pending patent applications;
- we were the first to file patent applications for these inventions;
- others will not develop similar or alternative technologies that do not infringe our patents;
- any of our patents will be found to ultimately be valid and enforceable;
- any patents issued to us will provide a basis for an exclusive market for our commercially viable products, will provide us with any competitive advantages or will not be challenged by third parties;
- we will develop additional proprietary technologies or product candidates that are separately patentable; or
- our commercial activities or products will not infringe upon the patents of others.

We rely upon unpatented trade secrets, unpatented know-how and continuing technological innovation to develop and maintain our competitive position, which we seek to protect, in part, by confidentiality agreements with employees, consultants, collaborators and vendors. We also have agreements with employees and selected consultants that obligate them to assign their inventions to us. It is possible that technology relevant to our business will be independently developed by a person who is not a party to such an agreement. We may not be able to prevent the unauthorized disclosure or use of our technical knowledge or trade secrets by consultants, collaborators, vendors, former employees and current employees. Furthermore, if the parties to our confidentiality agreements breach or violate the terms of these agreements, we may not have adequate remedies for any such breach or violation, and we could lose our trade secrets through such breaches or violations. Further, our trade secrets could otherwise become known or be independently discovered by our competitors.

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time-consuming and unsuccessful.

Competitors may infringe our patents or the patents of our licensors. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming and divert the attention of our management and key personnel from our business operations. Even if we prevail in any lawsuits that we initiate, the damages or other remedies awarded may not be commercially meaningful. In addition, in an infringement proceeding, a court may decide that a patent of ours or our licensors is not valid, is unenforceable and/or is not infringed, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our patent applications at risk of not issuing.

Interference proceedings provoked by third parties or brought by us may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our common stock.

We may infringe the intellectual property rights of others, which may prevent or delay our product development efforts and stop us from commercializing or increase the costs of commercializing setmelanotide, if approved.

Our success will depend in part on our ability to operate without infringing the intellectual property and proprietary rights of third parties. We cannot assure you that our business, products and methods do not or will not infringe the patents or other intellectual property rights of third parties. For example, numerous third-party U.S. and non-U.S. patents and pending applications exist that cover melanocortin receptor analogs and methods of using these analogs.

The pharmaceutical industry is characterized by extensive litigation regarding patents and other intellectual property rights. Other parties may allege that setmelanotide or the use of our technologies infringes patent claims or other intellectual property rights held by them or that we are employing their proprietary technology without authorization. For example, we received a letter in January 2013 from a third party bringing to our attention several patents and patent applications, both U.S. and non-U.S. We responded in April 2013 and have not received any further correspondence since then. All but a few of the patents and patent applications mentioned in the letter were abandoned or not in force at the time the letter was sent to us. Although subsequent to our response the third party has allowed all the remaining patents to lapse for non-payment of patent maintenance fees, we cannot assure you that the holder of these third-party patents will not attempt to assert these patents against us.

Patent and other types of intellectual property litigation can involve complex factual and legal questions, and their outcome is uncertain. Any claim relating to intellectual property infringement that is successfully asserted against us may require us to pay substantial damages, including treble damages and attorney's fees if we are found to be willfully infringing another party's patents, for past use of the asserted intellectual property and royalties and other consideration going forward if we are forced or choose to take a license. In addition, if any such claim were successfully asserted against us and we could not obtain such a license, we may be forced to stop or delay developing, manufacturing, selling or otherwise commercializing setmelanotide.

If we are unable to avoid infringing the patent rights of others, we may be required to seek a license, defend an infringement action or challenge the validity of the patents in court, or redesign our products. Patent litigation is costly and time consuming. We may not have sufficient resources to bring these actions to a successful conclusion.

In addition, in order to avoid infringing the intellectual property rights of third parties and any resulting intellectual property litigation or claims, we could be forced to do one or more of the following, which may not be possible and, even if possible, could be costly and time-consuming:

- cease development and commercialization of setmelanotide;

- pay substantial damages for past use of the asserted intellectual property;
- obtain a license from the holder of the asserted intellectual property, which license may not be available on reasonable terms, if at all; and
- in the case of trademark claims, rename setmelanotide.

Any of these risks coming to fruition could have a material adverse effect on our business, results of operations, financial condition and prospects.

We may be subject to claims challenging the inventorship or ownership of our patents and other intellectual property.

We may also be subject to claims that former employees, collaborators or other third parties have an ownership interest in our patents or other intellectual property. Litigation may be necessary to defend against these and other claims challenging inventorship or ownership. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, such intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

The U.S. Patent and Trademark Office, or U.S. PTO, and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other provisions during the patent process. There are situations in which noncompliance can result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, competitors might be able to enter the market earlier than would otherwise have been the case.

Issued patents covering setmelanotide could be found invalid or unenforceable if challenged in court.

If we or one of our licensing partners threatened or initiated legal proceedings against a third party to enforce a patent covering setmelanotide, the defendant could claim that the patent covering setmelanotide is invalid and/or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge include alleged failures to meet any one of several statutory requirements, including novelty, non-obviousness and enablement. Grounds for unenforceability assertions include allegations that someone connected with prosecution of the patent withheld material information from the U.S. PTO, or made a misleading statement, during patent prosecution. Third parties may also raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, *inter partes* review, post grant review and equivalent proceedings in foreign jurisdictions, for example, opposition proceedings. Such proceedings could result in revocation or amendment of our patents in such a way that they no longer cover setmelanotide or competitive products. The outcome following legal assertions of invalidity and/or unenforceability is unpredictable. With respect to validity, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on setmelanotide. Such a loss of patent protection would have a material adverse impact on our business.

We do not seek to protect our intellectual property rights in all jurisdictions throughout the world and we may not be able to adequately enforce our intellectual property rights even in the jurisdictions where we seek protection.

Filing, prosecuting and defending patents on setmelanotide in all countries and jurisdictions throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States could be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our product and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents and other intellectual property protection, particularly those relating to biopharmaceuticals, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. For example, an April 2017 report from the Office of the United States Trade Representative identified a number of countries, including India and China, where challenges to the procurement and enforcement of patent rights have been reported. Several countries, including India and China, have been listed in the report every year since 1989. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly, could put our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

We are dependent on licensed intellectual property. If we were to lose our rights to licensed intellectual property, we may not be able to continue developing or commercializing setmelanotide, if approved.

We have licensed our rights to setmelanotide from Ipsen Pharma SAS, or Ipsen. Our license with Ipsen imposes various obligations on us, and provides Ipsen the right to terminate the license in the event of our material breach of the license agreement, our failure to initiate or complete development of a licensed product, or our commencement of an action seeking to have an Ipsen licensed patent right declared invalid. Termination of our license from Ipsen would result in our loss of the right to use the licensed intellectual property, which would materially adversely affect our ability to develop and commercialize setmelanotide, as well as harm our competitive business position and our business prospects.

We also have licensed from Camurus its drug delivery technology, FluidCrystal, to formulate setmelanotide. Our license with Camurus imposes various obligations on us, and provides Camurus the right to terminate the license in the event of our material breach of the license agreement. Termination of our license from Camurus would result in our inability to use the licensed intellectual property.

We have licensed our rights to RM-853 from Takeda Pharmaceutical Company Limited, or Takeda. Our license with Takeda imposes various obligations on us, and provides Takeda the right to terminate the license in the event of our material breach of the license agreement, if we voluntarily or involuntarily file for bankruptcy, or for our bringing an action seeking to have a Takeda license patent right declared invalid.

Termination of our license from Takeda would result in our inability to use the licensed intellectual property.

Among other obligations under our agreement with Takeda, Takeda has a right of first negotiation under certain circumstances to sublicense the assets we acquired from Takeda in the territory of Japan. This right of first negotiation remains in effect until the earlier of five years from the date of the agreement, consummation of a change in control, or sublicense to a third party. This may delay or limit our ability to enter into certain transactions with respect to this product candidate.

We may enter into additional licenses to third-party intellectual property that are necessary or useful to our business. Future licensors may also allege that we have breached our license agreement and may accordingly seek to terminate our license with them. In addition, future licensors may have the right to terminate our license at will. Any termination could result in our loss of the right to use the licensed intellectual property, which could materially adversely affect our ability to develop and commercialize setmelanotide, if approved, as well as harm our competitive business position and our business prospects.

We have not yet registered trademarks for a commercial trade name for setmelanotide and failure to secure such registrations could adversely affect our business.

We have not yet registered trademarks for a commercial trade name for setmelanotide. Any future trademark applications may be rejected during trademark registration proceedings. Although we would be given an opportunity to respond to those rejections, we may be unable to overcome them. In addition, in the U.S. PTO and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive those proceedings. Moreover, any name we propose to use for setmelanotide in the United States must be approved by the FDA, regardless of whether we have registered it, or applied to register it, as a trademark. The FDA typically conducts a review of proposed product names, including an evaluation of potential for confusion with other product names. If the FDA objects to any of our proposed product names, we may be required to expend significant additional resources in an effort to identify a suitable substitute name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA.

If we do not obtain additional protection under the Hatch-Waxman Amendments and similar foreign legislation by extending the patent terms and obtaining product exclusivity for setmelanotide, our business may be materially harmed.

Depending upon the timing, duration and specifics of FDA marketing approval for setmelanotide, one or more of the U.S. patents we license may be eligible for limited patent term restoration under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent term restoration of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, we may not be granted an extension because of, for example, failure to apply within applicable deadlines, failure to apply prior to expiration of relevant patents or otherwise failure to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or restoration or the term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and our ability to generate revenues could be materially adversely affected.

While we believe that setmelanotide contains active ingredients that would be treated by the FDA as a new chemical entity, or a new drug product, and, therefore, if approved, should be afforded five years of marketing exclusivity, the FDA may disagree with that conclusion and may approve generic products within a period that is less than five years. Manufacturers may seek to launch these generic products following the expiration of the applicable marketing exclusivity period, even if we still have patent protection for setmelanotide. Competition that setmelanotide may face from generic versions could materially and adversely impact our future revenue, profitability and cash flows and substantially limit our ability to obtain a return on the investments we have made in setmelanotide.

If we fail to obtain an extension of patent protection under similar foreign legislation, where applicable, our competitors may obtain approval of competing products following our patent expiration, and our ability to generate revenues could be materially adversely affected in the foreign countries concerned.

Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our product.

The United States has enacted and is currently implementing the America Invents Act of 2011, wide-ranging patent reform legislation. Further, the U.S. Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain future patents, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the federal courts and the U.S. PTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents or future patents.

We may be subject to damages resulting from claims that we or our employees have wrongfully used or disclosed alleged trade secrets of their former employers.

Our employees have been previously employed at other biotechnology or pharmaceutical companies, including our competitors or potential competitors. We may be subject to claims that these employees or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of the former employers of our employees. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management. If we fail in defending such claims, in addition to paying money damages, we may lose valuable intellectual property rights or personnel. A loss of key personnel or their work product could hamper or prevent our ability to commercialize setmelanotide, which would materially adversely affect our commercial development efforts.

Risks Related to Regulatory Approval and Marketing of Setmelanotide and Other Legal Compliance Matters

Even if we complete the necessary clinical trials, the regulatory and marketing approval process is expensive, time consuming and uncertain and may prevent us from obtaining approvals for the commercialization of setmelanotide. We depend entirely on the success of setmelanotide, which is in Phase 3 clinical development for treatment of POMC deficiency obesity and LepR deficiency obesity. We cannot be certain that we will be able to obtain regulatory approval for, or successfully commercialize, setmelanotide. If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we will not be able to commercialize setmelanotide, and our ability to generate revenue will be materially impaired.

We currently have only one product candidate, setmelanotide, in clinical development, and our business depends entirely on its successful clinical development, regulatory approval and commercialization. We currently have no drug products for sale and may never be able to develop marketable drug products. Setmelanotide, which is currently in Phase 3 clinical development as a treatment for genetic deficiencies affecting the MC4 pathway, including POMC deficiency obesity and LepR deficiency obesity, and which expect to initiate Phase 3 clinical development in Bardet-Biedl syndrome and Alström syndrome in 2018, will require substantial additional clinical development, testing and regulatory approval before we are permitted to commence commercialization. The clinical trials of setmelanotide are, and the manufacturing and marketing of setmelanotide will be, subject to extensive and rigorous review and regulation by numerous government authorities in the United States and in other countries where we intend to test and, if approved, market setmelanotide. Before obtaining regulatory approvals for the commercial sale of any product candidate, we must demonstrate through non-clinical testing and clinical trials that the product candidate is safe and effective for use in each target indication. This process can take many years and approval, if any, may be conditional on post-marketing studies and surveillance, and will require the expenditure of substantial resources beyond our existing cash and the proceeds we raise from this offering. When a sponsor relies exclusively or predominantly on foreign clinical data, the FDA may require a showing that those data are applicable to the U.S. population and U.S. medical practice, which in some cases may require bridging studies or other evidence. Of the large number of drugs in development in the United States and in other countries, only a small percentage will successfully complete the FDA regulatory approval process or the equivalent process in foreign jurisdictions and will be commercialized. In addition, we have not discussed all of our proposed development programs with the FDA of the competent authorities of foreign jurisdictions. Accordingly, even if we are able to obtain the requisite financing to continue to fund our development and clinical trials, we cannot assure you that setmelanotide will be successfully developed or commercialized.

We are not permitted to market setmelanotide in the United States until we receive approval of an NDA from the FDA, or in any foreign jurisdictions until we receive the requisite approval from the competent authorities in such countries. We have two Phase 3 clinical trials underway, one each for the treatment of POMC deficiency obesity and LepR deficiency obesity, and plan to initiate a third combined Phase 3 trial for Bardet-Biedl syndrome and Alström syndrome by the end of 2018. Under our current development program, we plan to conduct a single Phase 3 clinical trial for POMC deficiency obesity. To date, in our ongoing discussions with the FDA, the agency has not asked for additional Phase 3 trials in POMC deficiency obesity, but the agency could still require us to conduct additional Phase 3 clinical trials for this indication. Moreover, for POMC deficiency obesity, the FDA has provided clear advice in the past, but could at any time alter its previous advice on many aspects of the trial—the small size, the primary and key secondary endpoints, the open label design, the amount of past medical history available on individual patients, the statistical analysis plan, the definition of clinically-relevant success for the protocol, entry of patients ages six or over —all of which may impact the timing and ability to obtain FDA approval. For example, the FDA asked us in December 2017 to switch the order of our primary and key secondary endpoints for weight in our POMC deficiency Phase 3 protocol. While this might be favorable as the new primary endpoint has increased statistical power—the ability to produce a positive study result—this change occurred after the Phase 3 trial had started and may result in additional complexities such as more attention to compliance and retention. There are other aspects of the trial for which we have not received advice from the FDA, such as the number of U.S. versus non-U.S. patients and the number of patients with POMC gene defects versus the number of patients with PCSK1 defects, which could also impact the timing of and our ability to obtain FDA approval. We have received FDA comments that indicate the Phase 3 program for LepR deficiency can be similar to POMC deficiency, but we have not yet discussed with the FDA the protocol for a Phase 3 program for LepR deficiency obesity in detail. Therefore, the timeline for enrollment, availability of data, and cost of conducting such trials are less certain, and could be less favorable than those applicable to the POMC deficiency obesity program. Similarly, the preliminary FDA advice on the design of the Bardet-Biedl syndrome and Alström syndrome combined clinical Phase 3 study could, at any time, be altered by the FDA, including for example, the size of the trial, the type and importance of endpoints, the length of the trial, the ability to combine the two indications, the inclusion of pediatric patients and pediatric efficacy endpoints, and the design for any placebo-controlled aspect of the trial.

In addition, the FDA and other equivalent competent authorities in foreign jurisdictions will expect for there to be little or no introduction of bias in the open-label Phase 3 trials. Accordingly, we proposed to the FDA that little, if any, efficacy data will be available to us in any form until the Phase 3 trials are complete.

The FDA or other regulatory authorities and other equivalent competent authorities in foreign jurisdictions will also require that we conduct one or more pivotal trials for each other indication sought. In addition, we are not sure if one or more Phase 3 trials would be required for approval in each other indications. The need and length of placebo-controlled data in these pivotal trials and the number of patients required for these approvals is also unclear.

We will determine in our own judgment if a non-pivotal trial meets "proof of concept" in each of these indications. There is no certainty that the FDA, other competent authorities, or outside investors will agree with our determination, which might have an impact on the ability to transition to Phase 3 studies.

In the EU we are currently conducting the Phase 3 clinical trial RM-493-012 in Germany, France, Belgium, and the United Kingdom for POMC deficiency obesity. We are also conducting this trial in Canada. On March 23, 2017, we received EMA scientific advice on the appropriateness and sufficiency of the non-clinical and clinical development programs to support an initial marketing authorization application in POMC deficiency obesity. The EMA scientific advice included preliminary advice on the clinical trial RM-493-012. The EMA expressed general support for the ongoing Phase 3 program in POMC deficiency obesity. The EMA advised that the regulatory strategy for a rare disorder is supported and that the EMA may have to rely on scarce data. The EMA also advised, however, that we need to consider whether full approval or approval under conditional or exceptional circumstances would be the most appropriate pathway for application for POMC deficiency obesity.

In the EU we are currently conducting the Phase 3 clinical trial RM-493-015 in Germany, France, Netherlands, and the United Kingdom, for LepR deficiency obesity. We are also conducting this study in the United States. We have not obtained EMA scientific advice for the LepR deficiency indication, nor have we obtained EMA scientific advice for the Bardet-Biedl syndrome or Alström syndrome indications.

Given the orphan status of setmelanotide for the treatment of POMC deficiency in the EU the marketing authorization application for a POMC deficiency obesity indication will likely be submitted via the centralized procedure. We will also have to obtain orphan status in the EU for LepR deficiency obesity. In addition, we have submitted a pediatric investigation plan, or PIP, for setmelanotide to the EMA Pediatric Committee, or PDCO, in 2017. On April 27, 2018, the PDCO adopted an opinion accepting the PIPs for Setmelanotide in the treatment of appetite and general nutritional disorders, including the deferral and the waiver requested by us.

We cannot assure you that the clinical trials we are conducting in the EU will be completed within this timeline. Similar to the United States, we are subject to comprehensive regulatory oversight by the EMA and the competent authorities of the individual EU member states where we are conducting our clinical trials. Failure by us or by any of our third party partners to comply with EU laws and the related national laws of individual EU member states governing the conduct of clinical trials may result in the suspension of clinical trials or in other administrative, civil or criminal penalties.

Our plan is to expand our internal clinical development operations and capabilities so that we can continue to enroll and manage our Phase 2 and Phase 3 clinical trials such that if the clinical trials are successful, we can file NDAs for POMC deficiency obesity and LepR deficiency obesity in the United States by 2019 or early 2020. We believe we have finalized the design, timing and size of our Phase 3 trial for POMC deficiency obesity with the FDA but we cannot assure you that the trial will not be subject to further modification or that it will be completed on time. In addition, obtaining approval of an NDA and the approval of a marketing authorization application from the European Commission is a complex, lengthy, expensive and uncertain process, and the FDA, EMA or equivalent competent authorities in foreign jurisdictions may delay, limit or deny approval of setmelanotide for many reasons, including, among others:

- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may disagree with our interpretation of data from clinical trials, or may change the requirements for approval even after it has reviewed and commented on the design for our clinical trials;

- we may not be able to demonstrate to the satisfaction of the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions that setmelanotide is safe and effective in treating obesity caused by certain genetic deficiencies affecting the MC4 pathway;
- the results of our clinical trials may not be interpretable or meet the level of statistical or clinical significance required by the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions for marketing approval. For example, the potential unblinding of setmelanotide studies due to easily identifiable adverse events may raise the concern that potential bias has affected the clinical trial results;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may disagree with the number, size, conduct or implementation of our clinical trials;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may require that we conduct additional clinical trials or pre-clinical studies;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions or the applicable foreign regulatory agency may identify deficiencies in our chemistry, manufacturing or controls of setmelanotide;
- the CROs that we retain to conduct our clinical trials may take actions outside of our control that materially adversely impact our clinical trials;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may find the data from preclinical studies and clinical trials insufficient to demonstrate that clinical and other benefits of setmelanotide outweigh its safety risks;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may disagree with our interpretation of data from our preclinical studies and clinical trials;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may not approve the formulation, labeling or specifications of setmelanotide;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may not accept data generated at our clinical trial sites;
- if and when our NDA or our marketing authorization application is submitted and reviewed by an advisory committee, the FDA, the EMA, or the equivalent competent authorities in foreign jurisdictions may have difficulties scheduling an advisory committee meeting in a timely manner or the advisory committee may recommend against approval of our application or may recommend that the FDA, the EMA, or the equivalent competent authorities in foreign jurisdictions may require, as a condition of approval, additional preclinical studies or clinical trials, limitations on approved labeling or distribution and use restrictions;
- the FDA may require development of a REMS as a condition of approval or post-approval, or may not agree with our proposed REMS or may impose additional requirements that limit the promotion, advertising, distribution, or sales of setmelanotide. In addition, the European Commission may grant only conditional approval marketing authorization or impose specific obligations as a condition for marketing authorization, or may require us to conduct post authorization safety studies as a condition of grant of marketing authorization;
- the FDA or other equivalent competent foreign regulatory agency may deem our manufacturing processes or our facilities or the facilities of our CMOs inadequate to preserve the identity, strength, quality, purity, or potency of our product; or
- the FDA, the European Commission, or the equivalent competent authorities in foreign jurisdictions may change its approval policies or adopt new regulations and guidance.

Any of these factors, many of which are beyond our control, could jeopardize our ability to obtain regulatory approval for and successfully market setmelanotide. Moreover, because our business is entirely dependent upon setmelanotide, any such setback in our pursuit of regulatory approval would have a material adverse effect on our business and prospects.

Our failure to obtain marketing approval in foreign jurisdictions would prevent setmelanotide from being marketed abroad, and any approval we are granted for setmelanotide in the United States would not assure approval of setmelanotide in foreign jurisdictions.

In order to market and sell setmelanotide and any other product candidate that we may develop in the EU and many other jurisdictions, we or our third-party collaborators must obtain separate marketing authorizations and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be sold in that country. We or these third parties may not obtain approvals from competent authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by competent authorities in other countries or jurisdictions, and approval by one competent authority outside the United States does not ensure approval by competent authorities in other countries or jurisdictions or by the FDA. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize setmelanotide in any market. Additionally, on June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the EU, commonly referred to as Brexit. On March 29, 2017, the country formally notified the EU of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. Since a significant proportion of the regulatory framework in the United Kingdom is derived from EU directives and regulations, the withdrawal of the United Kingdom from the EU could materially impact the regulatory regime with respect to the approval of setmelanotide in the United Kingdom or the EU. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing setmelanotide in the United Kingdom and/or the EU and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or EU for setmelanotide, which could significantly and materially harm our business.

Even if we obtain marketing approval for setmelanotide, the terms of approval and ongoing regulation may limit how we manufacture and market setmelanotide and compliance with such requirements may involve substantial resources, which could materially impair our ability to generate revenue.

Even if we receive marketing approval for setmelanotide, regulatory authorities may impose significant restrictions on setmelanotide's indicated uses or marketing or impose ongoing requirements for potentially costly post approval studies. Setmelanotide will also be subject to ongoing requirements by the FDA, the EMA, and the competent authorities in the EU member states, governing labeling, packaging, storage, advertising, promotion, marketing, distribution, importation, exportation, post-approval changes, manufacturing, recordkeeping, and submission of safety and other post market information. The FDA and the other competent foreign authorities have significant post market authority, including, for example, the authority to require labeling changes based on new safety information and to require post market studies or clinical trials to evaluate serious safety risks related to the use of a drug. The FDA also has the authority to require, as part of an NDA or post approval, the submission of a REMS, which may include Elements to Assure Safe Use, or ETASU. Any REMS required by the FDA may lead to increased costs to assure compliance with new post approval regulatory requirements and potential requirements or restrictions on the sale of approved products, all of which could lead to lower sales volume and revenue.

Manufacturers of drug products and their facilities are subject to continual review and periodic inspections by the FDA and other equivalent competent authorities for compliance with cGMPs and other regulations. If we or a regulatory agency discover problems with setmelanotide, such as adverse events of unanticipated severity or frequency, or problems with the facility where setmelanotide is manufactured, a regulatory agency may impose restrictions on setmelanotide, the manufacturer or us, including requiring withdrawal of setmelanotide from the market or suspension of manufacturing. If we or the manufacturing facilities for setmelanotide fail to comply with applicable regulatory requirements, a regulatory agency may, among other things:

- issue warning letters or untitled letters;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend or withdraw marketing approval;
- suspend any ongoing clinical trials;
- refuse to approve pending applications or supplements to applications submitted by us;
- suspend or impose restrictions on operations, including costly new manufacturing requirements; or
- seize or detain setmelanotide, refuse to permit the import or export of setmelanotide, or request that we initiate a product recall.

Accordingly, assuming we receive marketing approval for setmelanotide, we and our CMOs will continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance and quality control. If we are not able to comply with post-approval regulatory requirements, we could have the marketing approvals for setmelanotide withdrawn by regulatory authorities and our ability to market any future products could be limited, which could adversely affect our ability to achieve or sustain profitability. Thus, the cost of compliance with post-approval regulations may have a negative effect on our operating results and financial condition.

Similar to the United States, both marketing authorization holders and manufacturers of medicinal products are subject to comprehensive regulatory oversight by the EMA and the competent authorities of the individual EU member states, both before and after grant of the manufacturing and marketing authorizations. This oversight includes control of compliance with cGMP rules, which govern quality control of the manufacturing process and require documentation policies and procedures. We and our third party manufacturers would be required to ensure that all of our processes, methods, and equipment are compliant with cGMP. Failure by us or by any of our third party partners, including suppliers, manufacturers, and distributors to comply with EU laws and the related national laws of individual EU member states governing the conduct of clinical trials, manufacturing approval, marketing authorization of medicinal products, both before and after grant of marketing authorization, and marketing of such products following grant of authorization may result in administrative, civil, or criminal penalties. These penalties could include delays in or refusal to authorize the conduct of clinical trials or to grant marketing authorization, product withdrawals and recalls, product seizures, suspension, or variation of the marketing authorization, total or partial suspension of production, distribution, manufacturing, or clinical trials, operating restrictions, injunctions, suspension of licenses, fines, and criminal penalties.

In addition, EU legislation related to pharmacovigilance, or the assessment and monitoring of the safety of medicinal products, provides that the EMA and the competent authorities of the EU member states have the authority to require companies to conduct additional post-approval clinical efficacy and safety studies. The legislation also governs the obligations of marketing authorization holders with respect to additional monitoring, adverse event management and reporting. Under the pharmacovigilance legislation and its related regulations and guidelines, we may be required to conduct a labor intensive collection of data regarding the risks and benefits of marketed products and may be required to engage in ongoing assessments of those risks and benefits, including the possible requirement to conduct additional clinical studies, which may be time-consuming and expensive and could impact our profitability.

Non-compliance with such obligations can lead to the variation, suspension or withdrawal of marketing authorization or imposition of financial penalties or other enforcement measures.

Current and future healthcare reform legislation or regulation may increase the difficulty and cost for us and any future collaborators to obtain marketing approval of and commercialize setmelanotide and may adversely affect the prices we, or they, may obtain and may have a negative impact on our business and results of operations.

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could, among other things, prevent or delay marketing approval of setmelanotide, restrict or regulate post-approval activities and affect our ability, or the ability of any future collaborators, to profitably sell any products for which we, or they, obtain marketing approval. Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives. We expect that current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we, or any future collaborators, may receive for any approved products.

In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act of 2010, or collectively the ACA. Among the provisions of the ACA of importance to our business, including, without limitation, our ability to commercialize and the prices we may obtain for any product candidates and that are approved for sale, are the following:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs, although this fee does not apply to sales of certain products approved exclusively for orphan indications;

- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;

- expansion of manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs and revising the definition of "average manufacturer price," or AMP, for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices and extending rebate liability to prescriptions for individuals enrolled in Medicare Advantage plans;

- introduction of a price reporting requirement for drugs that are inhaled, instilled, implanted, injected, or infused and not generally dispensed through retail community pharmacies;

- addition of more entity types eligible for participation in the Public Health Service the 340B drug pricing program, or the 340B program;

- established the Medicare Part D coverage gap discount program by requiring manufacturers to provide a 50% point-of-sale-discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D;

- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;

- the Independent Payment Advisory Board, or IPAB, which has authority to recommend certain changes to the Medicare program to reduce expenditures by the program that could result in reduced payments for prescription drugs. However, the IPAB implementation has been not been clearly defined. ACA provided that under certain circumstances, IPAB recommendations or recommendations of the Secretary of Health and Human Services will become law unless Congress enacts legislation that will achieve the same or greater Medicare cost savings; and

- established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. For example, beginning April 1, 2013, Medicare payments for all items and services, including drugs and biologics, were reduced by 2% under the sequestration (i.e., automatic spending reductions) required by the Budget Control Act of 2011, as amended by the American Taxpayer Relief Act of 2012. Subsequent legislation extended the 2% reduction, on average, to 2025. Sequestration may result in additional reductions in Medicare and other healthcare funding and, if we obtain regulatory approvals, may otherwise affect the prices we may obtain for setmelanotide or the frequency with which setmelanotide is prescribed or used if approved.

Legislative changes to or regulatory changes under the ACA have occurred in the 115th U.S. Congress and under the Trump administration. For example, the Tax Cuts and Jobs Act enacted on December 22, 2017, eliminated the shared responsibility payment for individuals who fail to maintain minimum essential coverage under section 5000A of the Internal Revenue Code of 1986, as amended, or the Code, commonly referred to as the individual mandate, beginning in 2019. Further, in the Bipartisan Budget Act of 2018, the Medicare Part D coverage gap discount program was revised to increase drug manufacturers' discount levels under the program. Additional legislative changes to and regulatory changes under the ACA remain possible, but the nature and extent of such potential additional changes are uncertain at this time. We expect that the ACA, as currently enacted or as it may be amended in the future, and other healthcare reform measures that may be adopted in the future, could have a material adverse effect on our industry generally and on our ability to successfully commercialize our product candidates, if approved.

Additional changes that may affect our business include the expansion of new programs such as Medicare payment for performance initiatives for physicians under the Medicare Access and CHIP Reauthorization Act of 2015, or MACRA, which will be fully implemented in 2019. At this time, it is unclear how the introduction of the Medicare quality payment program will impact overall physician reimbursement. The costs of prescription pharmaceuticals in the United States has also been the subject of considerable discussion in the United States, and members of Congress and the Administration have stated that they will address such costs through new legislative and administrative measures. This focus has resulted in several Congressional inquiries and proposed bills designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products.

We expect that these and other healthcare reform measures that may be adopted in the future may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved drug. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our drugs. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our drug candidates or additional pricing pressures.

The pricing of prescription pharmaceuticals is also subject to governmental control outside the United States. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost effectiveness of setmelanotide to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our ability to generate revenues and become profitable could be impaired.

If we participate in the Medicaid Drug Rebate Program and fail to comply with our reporting and payment obligations under that program or other governmental pricing programs that we participate in, we could be subject to additional reimbursement requirements, penalties, sanctions and fines, which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

We expect to participate in and have certain price reporting obligations to the Medicaid Drug Rebate program. Under the Medicaid Drug Rebate program, if we successfully commercialize setmelanotide, we would be required to pay a rebate to each state Medicaid program for our covered outpatient drugs that are dispensed to Medicaid beneficiaries and paid for by a state Medicaid program as a condition of having federal funds being made available to the states for our drugs under Medicaid and Medicare Part B. Those rebates are based on pricing data we would have to report on a monthly and quarterly basis to the Centers for Medicare and Medicaid Services, or CMS, the federal agency that administers the Medicaid Drug Rebate program. These data include the average manufacturer price and, in the case of innovator products, the best price for each drug which, in general, represents the lowest price available from the manufacturer to any entity in the U.S. in any pricing structure, calculated to include all sales and associated rebates, discounts and other price concessions. Our failure to comply with these price reporting and rebate payment obligations if we participate in the program could negatively impact our financial results.

Federal law requires that any company that participates in the Medicaid Drug Rebate program also participate in the 340B program in order for federal funds to be available for the manufacturer's drugs under Medicaid and Medicare Part B. The 340B program requires participating manufacturers to agree to charge statutorily defined covered entities no more than the 340B "ceiling price" for the manufacturer's covered outpatient drugs. These 340B covered entities include a variety of community health clinics and other entities that receive health services grants from the Public Health Service, as well as hospitals that serve a disproportionate share of low-income patients. The ACA expanded the list of covered entities to include certain free-standing cancer hospitals, critical access hospitals, rural referral centers and sole community hospitals, but exempts "orphan drugs" from the ceiling price requirements for these covered entities. The 340B ceiling price is calculated using a statutory formula based on the average manufacturer price and rebate amount for the covered outpatient drug as calculated under the Medicaid Drug Rebate program, and in general, products subject to Medicaid price reporting and rebate liability are also subject to the 340B ceiling price calculation and discount requirement. Any additional future changes to the definition of average manufacturer price and the Medicaid rebate amount under the ACA or other legislation or regulation could affect our 340B ceiling price calculations and negatively impact our results of operations if we successfully commercialize setmelanotide. In addition, legislation may be introduced that, if passed, would further expand the 340B program to additional covered entities or would require participating manufacturers to agree to provide 340B discounted pricing on drugs used in an inpatient setting.

In order to be eligible to have our products that we successfully commercialize paid for with federal funds under the Medicaid program and purchased by certain federal agencies and grantees, we also would have to participate in the U.S. Department of Veterans Affairs, or VA, Federal Supply Schedule, or FSS, pricing program. As part of this program, we would be obligated to make our products available for procurement on an FSS contract under which we must comply with standard government terms and conditions and charge a price that is no higher than the statutory Federal Ceiling Price, or FCP, to four federal agencies (VA, U.S. Department of Defense, or DOD, Public Health Service, and U.S. Coast Guard).

Civil monetary penalties can be applied if we participate in these programs and if we are found to have knowingly submitted any false price information to the government or if we fail to submit the required price data on a timely basis. Such conduct also could be grounds for CMS to terminate the Medicaid drug rebate agreement pursuant to which we would participate in the Medicaid drug rebate program, in which case federal payments may not be available under Medicaid for our covered outpatient drugs. We cannot assure you that our submissions will not be found by CMS or another government agency to be incomplete or incorrect.

If we obtain marketing approval for setmelanotide, we will be subject to strict enforcement of post-marketing requirements and we could be subject to substantial penalties, including withdrawal of our product from the market, if we fail to comply with all regulatory requirements.

If we obtain marketing approval for setmelanotide, we will be subject to continual requirements of and review by the FDA and equivalent competent authorities in foreign jurisdictions. These requirements may include, but are not limited to, post-approval studies to be conducted which may include carcinogenicity studies, a QT interval prolongation study in one form or another, other Phase 1 trials, and ongoing natural history studies with patient registries. Other requirements may also include, among other things, restrictions governing promotion of an approved product, submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, and requirements regarding the distribution of samples to physicians and recordkeeping. The FDA and other federal and state agencies, including the Department of Justice and other equivalent competent authorities in foreign jurisdictions, closely regulate compliance with all requirements governing prescription drug products, including requirements pertaining to marketing and promotion of drugs in accordance with the provisions of the approved labeling and manufacturing of products in accordance with cGMP requirements. Violations of such requirements may lead to investigations alleging violations of the FDCA, and other statutes, including the False Claims Act and other federal and state health care fraud and abuse laws as well as state consumer protection laws.

For example, the FDA and other equivalent competent authorities in foreign jurisdictions strictly regulate the promotional claims that may be made about prescription products, such as setmelanotide, if approved. In particular, a product may not be promoted for uses that are not approved by the FDA or such other regulatory agencies as reflected in the product's approved labeling. If we receive marketing approval for setmelanotide as a treatment for obesity caused by certain genetic deficiencies affecting the MC4 pathway, physicians may nevertheless prescribe setmelanotide to their patients in a manner that is inconsistent with the approved labeling. If we are found to have promoted such off-label uses, we may become subject to significant liability. The federal government has levied large civil and criminal fines against companies for alleged improper promotion and has enjoined several companies from engaging in off-label promotion. The FDA has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed. Oversight and management of promotional practices may require operational changes and additions, if setmelanotide is approved and commercialized. If we cannot successfully manage the promotion of setmelanotide, if approved, we could become subject to significant liability, which would materially adversely affect our business and financial condition.

In the EU, the advertising and promotion of our products are subject to EU laws governing promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices. In addition, other legislation adopted by individual EU member states may apply to the advertising and promotion of medicinal products. These laws require that promotional materials and advertising in relation to medicinal products comply with the product's Summary of Product Characteristics, or SmPC, as approved by the competent authorities. The SmPC is the document that provides information to physicians concerning the safe and effective use of the medicinal product. It forms an intrinsic and integral part of the marketing authorization granted for the medicinal product. Promotion of a medicinal product that does not comply with the SmPC is considered to constitute off-label promotion. The off-label promotion of medicinal products is prohibited in the EU. The applicable laws at EU level and in the individual EU member states also prohibit the direct-to-consumer advertising of prescription-only medicinal products. Violations of the rules governing the promotion of medicinal products in the EU could be penalized by administrative measures, fines and imprisonment. These laws may further limit or restrict the advertising and promotion of our products to the general public and may also impose limitations on our promotional activities with health care professionals.

We may be subject to federal and state healthcare laws and regulations. If we are unable to comply or have not fully complied with such laws and regulations, we could face criminal sanctions, damages, civil penalties, reputational harm and diminished profits and future earnings.

Healthcare providers, physicians and others will play a primary role in the recommendation and prescription of setmelanotide, if approved. Our arrangements and interactions with healthcare professionals, third-party payors, patients and others will expose us to broadly applicable fraud and abuse, anti-kickback, false claims and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute setmelanotide, if we obtain marketing approval. The U.S. federal and state healthcare laws and regulations that may affect our ability to operate include, but are not limited to:

- The United States federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, or receiving remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, lease order or arranging for or recommending of the purchase, lease or order of any good or service for which payment may be made, in whole or in part, by federal healthcare programs such as Medicare and Medicaid. This statute has been interpreted to apply to arrangements between pharmaceutical companies on one hand and prescribers, purchasers and formulary managers on the other. Liability under the Anti-Kickback Statute may be established without proving actual knowledge of the statute or specific intent to violate it. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. Although there are a number of statutory exemptions and regulatory safe harbors to the federal Anti-Kickback Statute protecting certain common business arrangements and activities from prosecution or regulatory sanctions, the exemptions and safe harbors are drawn narrowly. Practices that involve remuneration to those who prescribe, purchase, or recommend pharmaceutical and biological products, including certain discounts, or engaging such individuals as consultants, advisors, or speakers, may be subject to scrutiny if they do not fit squarely within an exemption or safe harbor. Our practices may not in all cases meet all of the criteria for safe harbor protection from anti-kickback liability. Moreover, there are no safe harbors for many common practices, such as educational and research grants, charitable donations, product support and patient assistance programs.

- The federal civil False Claims Act prohibits individuals or entities from, among other things, knowingly presenting, or causing to be presented a false or fraudulent claim for payment of government funds, or knowingly making, using or causing to made or used a false record or statement material to an obligation to pay money to the government or knowingly concealing or knowingly and improperly avoiding, decreasing or concealing an obligation to pay money to the federal government. Actions under the False Claims Act may be brought by the Attorney General or as a qui tam action by a private individual in the name of the government. Many pharmaceutical manufacturers have been investigated and have reached substantial financial settlements with the federal government under the civil False Claims Act for a variety of alleged improper activities including causing false claims to be submitted as a result of the marketing of their products for unapproved and thus non-reimbursable uses, inflating prices reported to private price publication services which are used to set drug payment rates under government healthcare programs, and other interactions with prescribers and other customers including those that may have affected their billing or coding practices and submission to the federal government. The government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. Pharmaceutical and other healthcare companies also are subject to other federal false claims laws, including, among others, federal criminal healthcare fraud and false statement statutes that extend to non-government health benefit programs.

- The federal Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program and also imposes obligations, with respect to safeguarding the privacy, security and transmission of individually identifiable health information.

- HIPAA and the federal false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement or representation, or making or using any false writing or document knowing the same to contain any materially false, fictitious or fraudulent statement or entry in connection with the delivery of or payment for healthcare benefits, items or services.

- Numerous federal and state laws and regulations that address privacy and data security, including state data breach notification laws, state health information privacy laws, and federal and state consumer protection laws (e.g., Section 5 of the FTC Act), govern the collection, use, disclosure and protection of health-related and other personal information.

- The federal Physician Payments Sunshine Act, being implemented as the Open Payments Program, requires certain manufacturers of drugs, devices, biologics and medical supplies to report payments and other transfers of value to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Pharmaceutical and biological manufacturers with products for which payment is available under Medicare, Medicaid or the State Children's Health Insurance Program are required to submit a report to the Centers for Medicare and Medicaid Services within the U.S. Department of Health and Human Services on or before the 90th day of each calendar year disclosing reportable payments made in the previous calendar year.

- Analogous state laws and regulations, such as state anti-kickback and false claims laws, which may apply to items or services reimbursed under Medicaid and other state programs or, in several states, regardless of the payer. Some state laws require pharmaceutical companies to report expenses relating to the marketing and promotion of pharmaceutical products and to report gifts and payments to certain health care providers in those states. Some of these states also prohibit certain marketing-related activities including the provision of gifts, meals, or other items to certain health care providers. Some states restrict the ability of manufacturers to offer co-pay support to patients for certain prescription drugs. Other states and cities require identification or licensing of sales representatives. In addition, California, Connecticut, Nevada, and Massachusetts require pharmaceutical companies to implement compliance programs or marketing codes of conduct.

Ensuring that our business arrangements and interactions with healthcare professionals, third-party payors, patients and others comply with applicable healthcare laws and regulations will require substantial resources. Various state and federal regulatory and enforcement agencies continue actively to investigate violations of health care laws and regulations, and the United States Congress continues to strengthen the arsenal of enforcement tools. Most recently, the Bipartisan Budget Act of 2018 increased the criminal and civil penalties that can be imposed for violating certain federal health care laws, including the Anti-Kickback Statute. It is possible that governmental authorities will conclude that our business practices do not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations, including anticipated activities to be conducted by our sales and marketing team, were found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, imprisonment, damages, fines, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations, any of which could substantially disrupt our operations. Although compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. Any action against us for violation of these laws or regulations, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business.

Our employees may engage in misconduct or other improper activities, including violating applicable regulatory standards and requirements or engaging in insider trading, which could significantly harm our business.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with the regulations of the FDA and applicable non-U.S. regulators, provide accurate information to the FDA and applicable non-U.S. regulators, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee misconduct could also involve the improper use of, including trading on, information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter employee misconduct, and any precautions we take to detect and prevent this activity may be ineffective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions. Some of these laws and related risks are described under the risk factor "*We may be subject to federal and state healthcare laws and regulations. If we are unable to comply or have not fully complied with such laws and regulations, we could face criminal sanctions, damages, civil penalties, reputational harm and diminished profits and future earnings*" of this prospectus.

Our failure to comply with data protection laws and regulations could lead to government enforcement actions and significant penalties against us, and adversely impact our operating results.

We are subject to U.S. data protection laws and regulations (i.e., laws and regulations that address privacy and data security) at both the federal and state levels. The legislative and regulatory landscape for data protection continues to evolve, and in recent years there has been an increasing focus on privacy and data security issues. Numerous federal and state laws, including state data breach notification laws, state health information privacy laws, and federal and state consumer protection laws (e.g., Section 5 of the FTC Act), govern the collection, use, and disclosure and protection of health-related and other personal information. Failure to comply with data protection laws and regulations could result in government enforcement actions and create liability for us, which could include civil and/or criminal penalties, private litigation and/or adverse publicity that could negatively affect our operating results and business. In addition, we may obtain health information from third parties, such as research institutions with which we collaborate, that are subject to privacy and security requirements under HIPAA. Although we are not directly subject to HIPAA, other than potentially with respect to providing certain employee benefits, we could be subject to criminal penalties if we knowingly obtain or disclose individually identifiable health information maintained by a HIPAA covered entity in a manner that is not authorized or permitted by HIPAA.

EU member states, Switzerland and other countries have also adopted data protection laws and regulations, which impose significant compliance obligations. In the EU, the collection and use of personal health data is governed by the provisions of the General Data Protection Regulation, or GDPR. The GDPR became effective on May 25, 2018, repealing the Data Protection Directive and increasing our responsibility and liability in relation to the processing of personal data of EU subjects.

The GDPR, together with the national legislation of the EU member states governing the processing of personal data, impose strict obligations and restrictions on the ability to collect, analyze and transfer personal data, including health data from clinical trials and adverse event reporting. In particular, these obligations and restrictions concern the consent of the individuals to whom the personal data relates, the information provided to the individuals, the transfer of personal data out of the EU, security breach notifications, security and confidentiality of the personal data, and imposition of substantial potential fines for breaches of the data protection obligations. Data protection authorities from the different EU member states may interpret the GDPR and national laws differently and impose additional requirements, which add to the complexity of processing personal data in the EU. Guidance on implementation and compliance practices are often updated or otherwise revised.

With respect to the transfer of personal data out of the EU, the GDPR provides that the transfer of personal data to countries that are not considered by the European Commission to provide an adequate level of data protection, including the United States, is permitted only on the basis of complying with specific legal steps.

The judgment by the Court of Justice of the European Union in Case C-362/14 Maximillian Schrems v. Data Protection Commissioner, or the Schrems case, held that the Safe Harbor Framework, which was relied upon by many United States entities as a basis for transfer of personal data from the EU to the United States, was invalid. United States entities therefore, had only the possibility to rely on the alternate procedures for such data transfer provided in the EU Data Protection Directive.

On February 29, 2016, however, the European Commission announced an agreement with the United States Department of Commerce, or the DOC, to replace the invalidated Safe Harbor framework with a new "Privacy Shield." On July 12, 2016, the European Commission adopted a decision on the adequacy of the protection provided by the Privacy Shield. The Privacy Shield is intended to address the requirements set out by the Court of Justice of the European Union in the Schrems case. The Privacy Shield imposes more stringent obligations on companies, provides stronger monitoring and enforcement by the DOC and the Federal Trade Commission, and makes commitments on the part of public authorities regarding access to information. United States entities have been able to certify to the DOC their compliance with the privacy principles of the Privacy Shield since August 1, 2016 and rely on the Privacy Shield certification to transfer of personal data from the EU to the United States.

However, in October 2016, three French digital rights advocacy group, La Quadrature du Net, French Data Network and the Fédération FDN, brought an action for annulment of the European Commission decision on the adequacy of the Privacy Shield before the Court of Justice of the EU (Case T-738/16). The case is currently pending before the European Court of Justice. If the Court of Justice of the European Union invalidates the Privacy Shield, it will no longer be possible to rely on the Privacy Shield certification to transfer personal data from the EU to entities in the United States. Adherence to the Privacy Shield is not, however, mandatory. Entities based in the United States are permitted to rely either on their adherence to the Privacy Shield or on the other authorized means and procedures to transfer personal data provided by the GDPR.

Our failure to comply with these laws, or changes in the way in which these laws are implemented, could lead to government enforcement actions and significant penalties against us, and adversely impact our operating results. In particular, our failure to comply with our obligations under the GDPR, including any failure to adopt measures to ensure that we can continue to conduct the data processing activities that we have initiated in the EU before the GDPR entered into application could adversely impact the validity of data generated in our studies.

Our future growth depends, in part, on our ability to penetrate foreign markets, where we will be subject to additional regulatory burdens and other risks and uncertainties.

Our future profitability will depend, in part, on our ability to commercialize setmelanotide in foreign markets for which we intend to rely on collaborations with third parties. If we commercialize setmelanotide in foreign markets, we will be subject to additional risks and uncertainties, including:

- our customers' ability to obtain reimbursement for setmelanotide in foreign markets;
- our inability to directly control commercial activities because we are relying on third parties;
- the burden of complying with complex and changing foreign regulatory, tax, accounting and legal requirements;
- different medical practices and customs in foreign countries affecting acceptance in the marketplace;
- import or export licensing requirements;
- longer accounts receivable collection times;
- longer lead times for shipping;
- language barriers for technical training;
- reduced protection of intellectual property rights in some foreign countries;
- foreign currency exchange rate fluctuations; and
- the interpretation of contractual provisions governed by foreign laws in the event of a contract dispute.

Foreign sales of setmelanotide could also be adversely affected by the imposition of governmental controls, political and economic instability, trade restrictions and changes in tariffs.

Laws and regulations governing any international operations we may have in the future may preclude us from developing, manufacturing and selling setmelanotide outside of the United States and require us to develop and implement costly compliance programs.

If we expand our operations outside of the United States, we must dedicate additional resources to comply with numerous laws and regulations in each jurisdiction in which we plan to operate. The Foreign Corrupt Practices Act of 1977, or the FCPA, prohibits any U.S. individual or business from paying, offering, authorizing payment or offering anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of such third party in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with certain accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the company, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations.

Compliance with the FCPA is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the FCPA presents particular challenges in the pharmaceutical industry, because, in many countries, hospitals are operated by the government, and doctors and other hospital employees are considered foreign officials. Certain payments to hospitals in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions.

Various laws, regulations and executive orders also restrict the use and dissemination outside of the United States, or the sharing with certain non-U.S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. If we expand our presence outside of the United States, it will require us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing or selling certain product candidates and products outside of the United States, which could limit our growth potential and increase our development costs.

The failure to comply with laws governing international business practices may result in substantial civil and criminal penalties and suspension or debarment from government contracting. The Securities and Exchange Commission, or SEC, also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA's accounting provisions.

The results of the United Kingdom's referendum on withdrawal from the EU may have a negative effect on global economic conditions, financial markets and our business.

On March 29, 2017, the Government of the United Kingdom initiated the formal procedure of withdrawal from the EU. The procedure involves a two-year negotiation period in which the United Kingdom and the EU must conclude an agreement setting out the terms of the United Kingdom's withdrawal and the arrangements for the United Kingdom's future relationship with the EU. This negotiation period could be extended by a unanimous decision of the European Council, in agreement with the United Kingdom.

The referendum has created significant uncertainty concerning the future relationship between the United Kingdom and the EU. This includes the laws and regulations that will apply as the United Kingdom determines which EU laws to replace or replicate in the event of a withdrawal. From a regulatory perspective, the United Kingdom's withdrawal could result in significant complexity and risks. A basic requirement related to the grant of a marketing authorization for a medicinal product in the EU is the requirement that the applicant is established in the EU. Following withdrawal of the United Kingdom from the EU, marketing authorizations previously granted to applicants established in the United Kingdom may no longer be valid. Moreover, depending upon the exact terms of the United Kingdom's withdrawal, there is an arguable risk that the scope of a marketing authorization for a medicinal product granted by the European Commission pursuant to the centralized procedure would not, in the future, include the United Kingdom. In these circumstances, an authorization granted by the United Kingdom's competent authorities would always be required to place medicinal products on the United Kingdom market.

In addition, the laws and regulations that will apply after the United Kingdom withdraws from the EU may have implications for manufacturing sites that hold certification issued by the United Kingdom competent authorities. Our capability to rely on these manufacturing sites for products intended for the EU market would also depend upon the exact terms of the United Kingdom's withdrawal.

The United Kingdom referendum has also given rise to calls for the governments of other EU member states to consider withdrawal from the EU. These developments, or the perception that they could occur, have had and may continue to have a material adverse effect on global economic conditions and the stability of global financial markets. They may significantly reduce global market liquidity and restrict the ability of key market participants to operate in certain financial markets.

Risks Related to Preclinical Development and Clinical Development of RM-853

We have assumed sole responsibility for the global product development and commercialization of RM-853, which may distract our management team from pursuing regulatory approval of setmelanotide, and we may never complete preclinical development of RM-853 or file an IND with the FDA. Many of the risks we have faced in preclinical development and in clinical development of setmelanotide will also exist in preclinical development of RM-853 and clinical development, should we ever enter into clinical development of RM-853

In March 2018 we entered into a license agreement with Takeda Pharmaceutical Company Limited, which we refer to as Takeda, to develop and commercialize T-3525770, now known as RM-853. RM-853 is a potent, orally available ghrelin o-acyltransferase, or GOAT, inhibitor currently in preclinical development for PWS. Under the terms of the license agreement, we assumed sole responsibility for the global product development and commercialization of RM-853. This relationship may distract our management team from clinical development of setmelanotide and may require us to expend financial and other resources. PWS is a complex disease and companies have had difficulties in developing new therapies for PWS. In addition, many of the risks we have faced in preclinical development and in clinical development of setmelanotide will also exist in preclinical development of RM-853 and clinical development, should we ever enter into clinical development of RM-853, including, but not limited to:

- RM-853 may not succeed in preclinical toxicology studies or may not be accepted by the FDA under an IND;
- results from preclinical studies may not be predictive of later clinical trials of RM-853;
- Phase 1 studies may show that RM-853 has a significant toxicities or pharmacokinetics not supportive of proceeding in development;
- failures or delays in the commencement or completion of preclinical studies or clinical trials could result in increased costs to us and could delay, prevent or limit our ability to generate revenue and continue our business;
- RM-853 could cause undesirable side effects that could result in significant negative consequences, including the inability to enter clinical development or receive regulatory approval;
- experience by others suggest that PWS patients are high risk for adverse experiences and for this, and many other reasons, clinical trials in that population are extremely challenging;
- other risks related to regulatory approval, and if ever received, marketing and commercialization of RM-853;
- potential product liability exposure;
- an inability to protect our intellectual property related to RM-853;
- risks related to our dependence on third parties, including in manufacturing RM-853 and conducting preclinical studies and clinical trials of RM-853;
- the burden of complying with complex and changing foreign regulatory, tax, accounting and legal requirements; and
- competition from other therapies in development for the treatment of PWS may result in reduced availability of patients for our clinical studies, the possible requirement to achieve clinical meaningful efficacy above any treatment that is approved prior to RM-853, and the potential for increased scrutiny from payers related to the relative benefit of RM-853 versus other therapies should they be approved prior to RM-853.

Risks Related to Employee Matters and Managing Growth

Our future success depends on our ability to retain our key employees and consultants, and to attract, retain and motivate qualified personnel.

We are highly dependent on Keith M. Gottesdiener, M.D., our Chief Executive Officer and President, Hunter C. Smith, our Chief Financial Officer and Treasurer, Nithya Desikan, our Chief Commercial Officer, Lex H.T. Van der Ploeg, Ph.D., our Chief Scientific Officer, and Fred T. Fiedorek, M.D., our Chief Medical Officer. We have employment agreements with these individuals but any individual may terminate his or her employment with us at any time. The loss of their services might impede the achievement of our research, development and commercialization objectives. We also do not have any key-person life insurance on any of these key employees. We rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us and may not be subject to non-compete agreements. Recruiting and retaining qualified scientific personnel and sales and marketing personnel will also be critical to our success. We may not be able to attract and retain these personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific personnel from universities and research institutions. Failure to succeed in clinical trials may make it more challenging to recruit and retain qualified scientific personnel.

We will need to develop and expand our company, and we may encounter difficulties in managing this development and expansion, which could disrupt our operations.

We expect to increase our number of employees and the scope of our operations. In particular, we will need to transition from a research and development company to a commercial company. To manage our anticipated development and expansion, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Also, our management may need to divert a disproportionate amount of its attention away from their day-to-day activities and devote a substantial amount of time to managing these development activities. Due to our limited resources, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. This may result in weaknesses in our infrastructure, and give rise to operational mistakes, loss of business and commercial opportunities, loss of employees and reduced productivity among remaining employees. The physical expansion of our operations may lead to significant costs and may divert financial resources from other projects, such as the development of setmelanotide. If our management is unable to effectively manage our expected development and expansion, our expenses may increase more than expected, our ability to generate or increase our revenue could be reduced and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize setmelanotide, if approved, and compete effectively will depend, in part, on our ability to effectively manage the future development and expansion of our company.

In order to satisfy our obligations as a public company, we will need to hire additional qualified accounting and financial personnel with appropriate public company experience.

As a newly public company, we must establish and maintain effective disclosure and financial controls. We will need to continue to hire additional accounting and financial personnel with appropriate public company experience and technical accounting knowledge, and it may be difficult to recruit and retain such personnel. Even if we are able to hire appropriate personnel, our existing operating expenses and operations will be impacted by the direct costs of their employment and the indirect consequences related to the diversion of management resources from product development efforts.

Our internal computer systems, or those of our third-party CROs, CMOs or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of setmelanotide development programs.

Our internal computer systems and those of our third-party CROs, CMOs, and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our programs. For example, the loss of clinical trial data for setmelanotide could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of or damage to our data or applications or other data or applications relating to our technology or product candidate, or inappropriate disclosure of confidential or proprietary information, we could incur liabilities and the further development of setmelanotide could be delayed.

We may acquire businesses or products, form strategic alliances or create joint ventures in the future, and we may not realize their benefits.

We may acquire additional businesses or products, form strategic alliances or create joint ventures with third parties that we believe will complement or augment our existing business. If we acquire businesses with promising markets or technologies, we may not be able to realize the benefit of acquiring such businesses if we are unable to successfully integrate them with our existing operations and company culture. We may encounter numerous difficulties in developing, manufacturing and marketing any new products resulting from a strategic alliance, joint venture or acquisition that delay or prevent us from realizing their expected benefits or enhancing our business. We cannot assure you that, following any such acquisition, we will achieve the expected synergies to justify the transaction.

Risks Related to Our Common Stock and This Offering

The price of our common stock may be volatile and fluctuate substantially, which could result in substantial losses for purchasers of our common stock in this offering.

If you purchase shares in this offering, you may not be able to resell those shares at or above the public offering price. The trading price of the shares has fluctuated, and is likely to continue to fluctuate substantially. The trading price of our securities depends on a number of factors, including those described in this "Risk Factors" section, many of which are beyond our control and may not be related to our operating performance.

Since the shares were sold at our initial public offering in October 2017 at a price of $17.00 per share, the price per share has ranged as low as $16.80 and as high as $34.99 through June 15, 2018. The market price of shares of our common stock could be subject to wide fluctuations in response to many risk factors listed in this section, and others beyond our control, including:

- results of preclinical and clinical trials of our products and product candidates, including setmelanotide and RM-853;
- results of clinical trials of our competitors' products;
- regulatory actions with respect to our products or our competitors' products;
- actual or anticipated fluctuations in our financial condition and operating results;
- publication of research reports by securities analysts about us or our competitors or our industry;
- our failure or the failure of our competitors to meet analysts' projections or guidance that we or our competitors may give to the market;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;

- additions and departures of key personnel;
- strategic decisions by us or our competitors, such as acquisitions, collaborations, divestitures, spin-offs, joint ventures, strategic investments or changes in business strategy;
- the passage of legislation or other regulatory developments in the United States and other countries affecting us or our industry;
- fluctuations in the valuation of companies perceived by investors to be comparable to us;
- sales of our common stock by us, our insiders or our other stockholders;
- speculation in the press or investment community;
- announcement or expectation of additional financing efforts;
- changes in accounting principles;
- changes in the structure of healthcare payment systems;
- terrorist acts, acts of war or periods of widespread civil unrest;
- natural disasters and other calamities;
- changes in market conditions for pharmaceutical and biopharmaceutical stocks;
- changes in general market, industry and economic conditions; and
- the other factors described in this "Risk Factors" section.

In addition, the stock market has experienced significant volatility, particularly with respect to pharmaceutical, biotechnology and other life sciences company stocks. The volatility of pharmaceutical, biotechnology and other life sciences company stocks often does not relate to the operating performance of the companies represented by the stock. In the past, securities class action litigation has often been initiated against companies following periods of volatility in their stock price. This type of litigation could result in substantial costs and divert our management's attention and resources, and could also require us to make substantial payments to satisfy judgments or to settle litigation

Our principal stockholders and management own a significant percentage of our stock and will be able to exert significant control over matters subject to stockholder approval.

Based on the number of shares outstanding as of March 31, 2018, our executive officers, directors, holders of 5% or more of our capital stock and their respective affiliates beneficially owned approximately 74% of our voting stock. These stockholders will have the ability to influence us through this ownership position. These stockholders may be able to determine all matters requiring stockholder approval. For example, these stockholders may be able to control elections of directors, amendments of our organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may feel are in your best interest as one of our stockholders.

Anti-takeover provisions in our charter documents and under Delaware law could make an acquisition of us, even one that may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

We are a Delaware corporation. Provisions in our amended and restated certificate of incorporation and amended and restated bylaws may delay or prevent an acquisition of us or a change in our management. In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which limits the ability of stockholders owning in excess of 15% of our outstanding voting stock to merge or combine with us. Although we believe these provisions collectively will provide for an opportunity to obtain greater value for stockholders by requiring potential acquirers to negotiate with our board of directors, they would apply even if an offer rejected by our board were considered beneficial by some stockholders. In addition, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors, which is responsible for appointing the members of our management. Any provision in our amended and restated certificate of incorporation and amended and restated bylaws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

An active market for our common stock may not be maintained.

Our stock only recently began trading on the Nasdaq Global Market and we can provide no assurance that we will be able to maintain an active trading market on the Nasdaq Global Market or any other exchange in the future. If an active market for our common is not maintained, it may be difficult for our stockholders to sell shares without depressing the market price for the shares or at all. An inactive market may also impair our ability to raise capital by selling shares and may impair our ability to acquire other businesses, applications or technologies using our shares as consideration.

Market volatility may affect our stock price and the value of your investment.

The market price for our common stock has been volatile and may continue to fluctuate significantly in response to a number of factors, most of which we cannot control, including, among others:

- plans for, progress of, or results from preclinical studies and clinical trials of setmelanotide;
- the failure of the FDA to approve setmelanotide;
- announcements of new products, technologies, commercial relationships, acquisitions or other events by us or our competitors;
- the success or failure of other weight loss therapies and companies targeting rare diseases and orphan drug treatment;
- regulatory or legal developments in the United States and other countries;
- failure of setmelanotide, if approved, to achieve commercial success;
- fluctuations in stock market prices and trading volumes of similar companies;
- general market conditions and overall fluctuations in U.S. equity markets;
- variations in our quarterly operating results;
- changes in our financial guidance or securities analysts' estimates of our financial performance;
- changes in accounting principles;
- our ability to raise additional capital and the terms on which we can raise it;
- sales of large blocks of our common stock, including sales by our executive officers, directors and significant stockholders;
- additions or departures of key personnel;
- discussion of us or our stock price by the press and by online investor communities; and
- other risks and uncertainties described in these risk factors.

Our quarterly operating results may fluctuate significantly.

We expect our operating results to be subject to quarterly fluctuations. Our net loss and other operating results will be affected by numerous factors, including:

- variations in the level of expenses related to our development programs;
- addition or termination of clinical trials;
- any intellectual property infringement lawsuit in which we may become involved;
- regulatory developments affecting setmelanotide;
- our execution of any collaborative, licensing or similar arrangements, and the timing of payments we may make or receive under these arrangements;
- the achievement and timing of milestone payments under our existing collaboration and license agreements; and
- if setmelanotide receives regulatory approval, the level of underlying demand for that product and customers' buying patterns.

If our quarterly operating results fall below the expectations of investors or securities analysts, the price of our common stock could decline substantially. Furthermore, any quarterly fluctuations in our operating results may, in turn, cause the price of our stock to fluctuate substantially.

We will have broad discretion in how we use the proceeds from this offering. We may not use these proceeds effectively, which could affect our results of operations and cause our stock price to decline.

We have considerable discretion in the application of the net proceeds from this offering. We intend to continue to use the net proceeds to fund development and manufacturing of setmelanotide through completion of our Phase 3 clinical trials and subsequent NDA submissions with the FDA for the treatment of POMC deficiency obesity and LepR deficiency obesity, the development of setmelanotide through our Phase 2 proof of concept clinical trials for Bardet-Biedl syndrome, Alström syndrome, POMC heterozygous deficiency obesity and POMC epigenetic disorders, as well as the initiation of our Phase 3 clinical trials for Bardet-Biedl syndrome and Alström syndrome, the preparation for commercialization of setmelanotide, initiatives to expand the diagnosis of genetic obesity, including research and scientific exchange related to our ongoing genotyping and genetic epidemiology studies and for working capital and administrative expenses, additional research and development expenses, and other general corporate purposes. As a result, investors will be relying upon management's judgment with only limited information about our specific intentions for the use of the net proceeds. We may use the net proceeds for purposes that do not yield a significant return or any return at all for our stockholders. In addition, pending their use, we may invest the net proceeds in a manner that does not produce income or that loses value.

Our ability to use certain net operating loss carryovers and other tax attributes may be limited.

We have incurred substantial losses during our history and we do not expect to become profitable in the near future and may never achieve profitability. Under the Code, a corporation is generally allowed a deduction for net operating losses, or NOLs, carried over from a prior taxable year. Under the Code, we can carry forward certain NOLs of our subsidiaries to offset future taxable income, if any, until such losses are used or, for NOLs arising in taxable years ending on or before December 31, 2017, until such NOLs expire. NOLs arising in taxable years ending after December 31, 2017 are not subject to expiration. NOLs arising in taxable years beginning after December 31, 2017 may only be used to offset up to 80% of the corporation's taxable income computed without taking into account NOL deductions. Other unused tax attributes, such as research tax credits may also be carried forward to offset future taxable income, if any, until such credits are used or expire. As of December 31, 2017, we had approximately $73.1 million and

$3.8 million of unused federal and state carryforwards of NOLs, respectively, and approximately $1.9 million and $0.5 million of unused federal and state carryforwards of tax credits, respectively. Additionally, as of December 31, 2017, we had federal orphan drug credits related to qualifying research of $2.3 million.

If a corporation undergoes an "ownership change," generally defined as a greater than 50% change by value in its equity ownership over a three-year period, Sections 382 and 383 of the Code limit the corporation's ability to use carryovers of its pre-change NOLs, credits and certain other tax attributes to reduce its tax liability for periods after the ownership change. Our issuance of common stock pursuant to our IPO may result in a limitation under Code Sections 382 and 383, either separately or in combination with certain prior or subsequent shifts in the ownership of our common stock. As a result, our ability to use carryovers of pre-change NOLs and credits to reduce our future U.S. federal income tax liability may be subject to limitations. This could result in increased U.S. federal income tax liability for us if we generate taxable income in a future period. Limitations on the use of NOLs and other tax attributes could also increase our state tax liability. Any such limitation could have a material adverse effect on our results of operations in future years. We have not completed a study to assess whether an ownership change for purposes of Section 382 or 383 has occurred, or whether there have been multiple ownership changes since our inception, due to the significant costs and complexities associated with such study.

The use of our tax attributes will also be limited to the extent that we do not generate positive taxable income in future tax periods. We do not expect to generate positive taxable income in the near future and we may never achieve tax profitability.

Raising additional capital may cause dilution to our existing stockholders, restrict our operations or require us to relinquish rights.

We may seek additional capital through a combination of private and public equity offerings, debt financings, collaborations and strategic and licensing arrangements. To the extent that we raise additional capital through the sale of common stock or securities convertible or exchangeable into common stock, a stockholder's ownership interest in our company will be diluted. In addition, the terms of any such securities may include liquidation or other preferences that materially adversely affect the rights of our stockholders. Debt financing, if available, would increase our fixed payment obligations and may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through collaboration, strategic partnerships and licensing arrangements with third parties, we may have to relinquish valuable rights to setmelanotide, our intellectual property or future revenue streams, or grant licenses on terms that are not favorable to us.

Substantial future sales or perceived potential sales of our common stock in the public market could cause the price of our common stock to decline significantly.

Sales of our common stock in the public market, or the perception that these sales could occur, could cause the market price of our common stock to decline significantly. Upon completion of this offering, we will have 31,885,367 shares of common stock outstanding, assuming the underwriters do not exercise their option to purchase additional shares. Upon completion of this offering, approximately 886,112 shares of our common stock beneficially owned by our executive officers and directors will be subject to lock-up agreements that prohibit, subject to certain exceptions, the disposal of any shares of our common stock or securities convertible into or exchangeable for shares of our common stock for a period of 90 days after the date of this prospectus and approximately 11,590,135 shares of our common stock beneficially owned by certain shareholders will be subject to similar restrictions for a period of 60 days after the date of this prospectus. Any or all of these shares may be released prior to the expiration of the lock-up period at the discretion of the designated representatives. To the extent shares are released before the expiration of the lock-up period and sold into the market, the market price of our common stock could decline significantly.

All of the shares sold in this offering and the remaining shares not subject to the lock-up period will be freely tradeable.

The holders of approximately 18.9 million shares of our common stock, or approximately 69% of our total outstanding common stock as of March 31, 2018, are entitled to rights with respect to the registration of their shares under the Securities Act, subject to vesting schedules. Registration of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act, except for shares purchased by affiliates. Any sales of securities by these stockholders could have a material adverse effect on the trading price of our common stock.

We are an "emerging growth company," and as a result of the reduced disclosure and governance requirements applicable to emerging growth companies, our common stock may be less attractive to investors.

We are an "emerging growth company" as defined in the JOBS Act, and we intend to take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies including, but not limited to, not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, as amended, or Section 404, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved. If we choose not to comply with the auditor attestation requirements of Section 404, our auditors will not be required to attest to the effectiveness of our internal control over financial reporting. As a result, investors may become less comfortable with the effectiveness of our internal controls and the risk that material weaknesses or other deficiencies in our internal controls go undetected or may increase. If we choose to provide reduced disclosures in our periodic reports and proxy statements while we are an emerging growth company, investors would have access to less information and analysis about our executive compensation, which may make it difficult for investors to evaluate our executive compensation practices. We cannot predict if investors will find our common stock less attractive because we will rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile. We may take advantage of these reporting exemptions until we are no longer an "emerging growth company." We will remain an "emerging growth company" until the earlier of (1) December 31, 2022, (2) the last day of the fiscal year (a) in which we have total annual gross revenue of at least $1.07 billion, or (b) in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeds $700 million as of the prior June 30th, and (3) the date on which we have issued more than $1.0 billion in non-convertible debt during the prior three-year period.

For as long as we remain an emerging growth company, we may take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not applicable to emerging growth companies as described in the preceding risk factor.

Pursuant to Section 404 of Sarbanes-Oxley, we will be required to furnish a report by our management on our internal control over financial reporting. However, while we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective as required by Section 404. If we identify one or more material weaknesses in our internal control over financial reporting, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

We may be at an increased risk of securities class action litigation.

Historically, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biotechnology and pharmaceutical companies have experienced significant stock price volatility in recent years. If we were to be sued, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

We do not intend to pay dividends on our common stock and, consequently, your ability to achieve a return on your investment will depend on appreciation in the price of our common stock.

We have never declared or paid any cash dividends on our common stock and do not currently intend to do so in the foreseeable future. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends in the foreseeable future. Therefore, the success of an investment in shares of our common stock will depend upon any future appreciation in their value. There is no guarantee that shares of our common stock will appreciate in value or even maintain the price at which you purchased them.

If you purchase our common stock in this offering, you will incur immediate and substantial dilution in the net tangible book value of your shares.

The public offering price of our common stock will be substantially higher than the net tangible book value per share of common stock. Therefore, if you purchase shares of our common stock in this offering, you will pay a price per share that substantially exceeds our net tangible book value per share after this offering. Based on the assumed public offering price of $32.60 per share, which is the last reported sale price of our common stock on the Nasdaq Global Market on June 15, 2018, you will experience immediate dilution of $24.01 per share, representing the difference between our as adjusted net tangible book value per share after giving effect to this offering and the assumed public offering price. Furthermore, if the underwriters exercise their option to purchase shares or our previously issued options to acquire common stock at prices below the assumed public offering price are exercised, you will experience further dilution. See "*Dilution*" for a more detailed description of the dilution to new investors in the offering.

If securities or industry analysts do not publish research or reports or publish unfavorable research or reports about our business, our stock price and trading volume could decline.

The trading market for our common stock will depend in part on the research and reports that securities or industry analysts publish about us, our business, our market or our competitors. We do not control these analysts. We do not currently have and may never obtain research coverage by securities and industry analysts. If no securities or industry analysts commence coverage of our company, the trading price for our stock would be negatively impacted. In the event we obtain securities or industry analyst coverage, if one or more of the analysts who covers us downgrades our stock, our stock price would likely decline. If one or more of these analysts issues unfavorable commentary or ceases to cover us or fails to regularly publish reports on us, interest in our stock could decrease, which could cause our stock price or trading volume to decline.

Unfavorable global economic conditions could adversely affect our business, financial condition or results of operations.

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets. The global financial crisis caused extreme volatility and disruptions in the capital and credit markets. A severe or prolonged economic downturn, such as the global financial crisis, could result in a variety of risks to our business, including weakened demand for setmelanotide and our ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy could also strain our suppliers, possibly resulting in supply disruption, or cause our customers to delay making payments for our services. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business.

We will continue to incur substantial costs as a result of operating as a public company, and our management will continue to devote substantial time to new compliance initiatives and corporation governance policies.

As a public company, and particularly after we are no longer an emerging growth company, we will continue to incur significant legal, accounting and other expenses. The Sarbanes-Oxley Act of 2002, or Sarbanes-Oxley, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of the Nasdaq Global Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will continue to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will continue to increase our legal and financial compliance costs and make some activities more time-consuming and costly.

We cannot predict or estimate the amount of additional costs we may incur or the timing of such costs. These rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

For as long as we remain an emerging growth company, we may take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not applicable to emerging growth companies as described in the preceding risk factor.

Pursuant to Section 404 of Sarbanes-Oxley, we will be required to furnish a report by our management on our internal control over financial reporting. However, while we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective as required by Section 404. If we identify one or more material weaknesses in our internal control over financial reporting, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus contains forward-looking statements, which reflect our current views with respect to, among other things, our operations and financial performance. You can identify these forward-looking statements by the use of words such as "outlook," "believes," "expects," "potential," "continues," "may," "will," "should," "seeks," "approximately," "predicts," "intends," "plans," "estimates," "anticipates" or the negative version of these words or other comparable words. Such forward-looking statements are subject to various risks and uncertainties. Accordingly, there are or will be important factors that could cause actual outcomes or results to differ materially from those indicated in these statements. We believe these factors include but are not limited to those described under "*Risk Factors*" and include, among other things:

- the success, cost and timing of our product development activities and clinical trials;
- our ability to obtain and maintain regulatory approval for setmelanotide and our future product candidates, if any, and any related restrictions, limitations, and/or warnings in the label of an approved product candidate;
- our ability to obtain funding for our operations;
- the commercialization of setmelanotide, if approved;
- the number of people in our target patient population;
- our plans to research, develop and commercialize setmelanotide;
- our ability to operate, and the implementation of our business strategy, as an independent company;
- our ability to attract collaborators with development, regulatory and commercialization expertise;
- our expectations regarding our ability to obtain and maintain intellectual property protection for setmelanotide;
- future agreements with third parties in connection with the commercialization of setmelanotide or our future product candidates, if any;
- the size and growth potential of the markets for setmelanotide, and our ability to serve those markets;
- our expectations for the pricing of setmelanotide;
- the rate and degree of market acceptance of setmelanotide, as well as the reimbursement coverage for setmelanotide;
- regulatory developments in the United States, the European Union and other jurisdictions;
- the performance of our third-party suppliers and manufacturers;
- the extent and success of competing therapies that are or may become available;
- our ability to attract and retain key scientific or management personnel;
- the accuracy of our estimates regarding our target patient populations, expenses, future revenues, capital requirements and needs for additional financing;
- our expectations regarding the period during which we qualify as an emerging growth company under the JOBS Act; and
- our use of the proceeds from this offering.

These factors should not be construed as exhaustive and should be read in conjunction with the other cautionary statements that are included in this prospectus. We undertake no obligation to publicly update or review any forward-looking statement, whether as a result of new information, future developments or otherwise.

MARKET, INDUSTRY AND OTHER DATA

This prospectus includes market, industry and other data and forecasts that we have derived from independent consultant reports, publicly available information, various industry publications, other published industry sources and our internal data and estimates. Independent consultant reports, industry publications and other published industry sources generally indicate that the information contained therein was obtained from sources believed to be reliable.

Due to the rarity of our target indications, there is no comprehensive patient registry or other method of establishing with precision the actual number of patients with MC4 pathway deficiencies. As a result, we have had to rely on other available sources to derive prevalence estimates for our target indications. Since the published epidemiology studies for these genetic deficiencies are based on relatively small population samples, and are not amenable to robust statistical analyses, it is possible that these projections may significantly exceed the addressable population, particularly given the need to genotype patients to definitively confirm a diagnosis.

We have estimated the potential addressable patient populations with these disorders based on the following sources and assumptions:

- *POMC Deficiency Obesity.* There are approximately 50 patients with POMC deficiency obesity noted in a series of published case reports, each mostly reporting a single or small number of patients. However, we believe our addressable patient population for this deficiency may be approximately 100 to 500 patients in the United States, and a comparable addressable patient population in Europe, as most of the reported cases are from a small number of academic research centers, and because genetic testing for POMC deficiency is often unavailable and currently is rarely performed. Based on discussions with experts in rare diseases, we also believe the number of diagnosed cases could increase several-fold with increased awareness of this deficiency and the availability of new treatments.

- *LepR Deficiency Obesity and POMC Heterozygous Deficiency Obesity.* Our addressable patient population estimate for LepR deficiency obesity is approximately 500 to 2,000 patients in the United States, and for POMC heterozygous deficiency obesity is approximately 4,000 patients in the United States, with a comparable addressable patient population for both indications in Europe. Our estimates are based on:

  - epidemiology studies on LepR deficiency and POMC heterozygous deficiency in small cohorts of patients comprised of children with severe obesity and adults with severe obesity who have a history of early onset obesity;

  - U.S. Census Bureau figures for adults and children, and Centers for Disease Control and Prevention, or CDC, prevalence numbers for severe adult obese patients (body mass index, or BMI, greater than 40 kg/ m^2) and for severe early onset obese children (99th percentile at ages two to 17 years old); and

  - with wider availability of genetic testing expected for LepR deficiency and POMC heterozygous deficiency and increased awareness of new treatments, our belief that up to 40% of patients with these disorders may eventually be diagnosed.

  Using these sources and assumptions, we calculated our estimates for addressable populations by multiplying (x) our estimate of the number of patients comprised of children with severe obesity and our estimate of a projected number of adults with severe obesity who have a history of early onset obesity, (y) the estimated prevalence from epidemiology studies of approximately 1% for LepR deficiency and 2% for POMC heterozygous, and (z) our estimated diagnosis rate of up to 40%.

- *Bardet-Biedl Syndrome.* Our addressable patient population estimate for Bardet-Biedl syndrome is approximately 1,500 to 2,500 patients in the United States based on:

  - published prevalence estimates of one in 100,000 in North America, which projects to approximately 3,250 people in the United States. We believe the majority of these patients are addressable patients; and

  - we believe that with wider availability of genetic testing expected for Bardet-Biedl syndrome and increased awareness of new treatments, the number of patients diagnosed with this disorder will increase.

- *Alström Syndrome.* Our addressable patient population estimate for Alström syndrome is approximately 500 to 1,000 patients worldwide. This estimate is based on:

  - published prevalence estimates of one in 1,000,000 in North America, which projects to approximately 325 people in the United States. We believe the majority of these patients are addressable patients; and

  - we believe that with wider availability of genetic testing expected for Alström syndrome and increased awareness of new treatments, the number of patients diagnosed with this disorder will increase.

- *POMC Epigenetic Disorders.* There is currently no epidemiology data that defines the prevalence of POMC epigenetic disorders.

We believe that the patient populations in the European Union are at least as large as those in the United States. However, we do not have comparable epidemiological data from the European Union and these estimates are therefore based solely on applying relative population percentages to the Company-derived estimates described above.

We are conducting additional clinical epidemiology studies to strengthen these prevalence projections. In parallel, we have developed a patient registry for diagnosed patients with POMC deficiency and LepR deficiency (and other genetic disorders of obesity) which will further inform prevalence projections for these rare genetic orders. See "*Business—Other Clinical and Scientific Initiatives in Genetic Obesity—Genotyping Study.*" for additional information.

Another method to estimate the size of these ultra-rare populations by genetic epidemiology is using newly available large genomic databases, containing full genome sequencing or exome sequencing. Ultra-rare orphan diseases are generally categorized as those that affect fewer than 20 patients per million. We have begun some substantial efforts with a series of such databases and/or collaborators. Much of our preliminary work has been with a database of approximately 140,000 genomes, which is representative of the U.S. population. These efforts generally are based on the prevalence of heterozygous mutations, as true null mutations are ultra-rare, and then standard scientific methods such as the Hardy-Weinberg equilibrium calculations, are applied to estimate the prevalence in the U.S. population. These methods make assumptions that may not be sufficiently robust for ultra-rare genetic disorders, and have the inherent variability of estimates for rare events. In addition, the databases currently available only provide limited clinical data, such as, age, weight and BMI, that would be needed to associate genetic defects with severe obesity. Our continued investigations support that the genetic epidemiological estimates are larger than the clinical epidemiological estimates, but we will likely need to reconcile the scientific definition of mutations with the regulatory definition. We believe the separate analyses that we have completed using clinical epidemiology and genetic epidemiology provide a robust range of patient population estimates for these rare disorders. However, to be conservative, we reference the clinical epidemiology figures in our descriptions of our target indications.

See "*Risk Factors—Risks Related to the Development of Setmelanotide—The number of patients suffering from each of the MC4 pathway deficiencies we are targeting is small and has not been established with precision. If the actual number of patients is smaller than we estimate, our revenue and ability to achieve profitability may be materially adversely affected.*" for additional information.

USE OF PROCEEDS

We estimate that the net proceeds to us from the sale of the shares of our common stock offered by us will be approximately $140.3 million, assuming a public offering price of $32.60 per share, which is the last reported sale price of our common stock on the Nasdaq Global Market on June 15, 2018, after deducting underwriting discounts and commissions and estimated offering expenses payable by us. If the underwriters' option to purchase additional shares in this offering is exercised in full, we estimate that our net proceeds will be approximately $161.4 million, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

A $1.00 increase or decrease in the assumed public offering price of $32.60 per share, which was the last reported sale price of our common stock on the Nasdaq Global Market on June 15, 2018, would increase or decrease our net proceeds from this offering by approximately $4.3 million, assuming that the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. An increase or decrease of 1,000,000 in the number of shares offered by us, as set forth on the cover page of this prospectus, would increase or decrease our net proceeds from this offering by approximately $30.6 million, assuming no change in the assumed public offering price per share, and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

As of March 31, 2018, we had cash and cash equivalents and short-term investments of approximately $136.5 million. We intend to use the net proceeds from this offering, together with our existing cash resources, as follows:

- approximately $42 million for the development of setmelanotide through the completion of our Phase 3 studies in POMC deficiency obesity and LepR deficiency obesity, as well as preparation for regulatory filing for these indications and initial preparation for the commercialization of setmelanotide in the United States;

- approximately $10 million for the development of setmelanotide through the completion of our Phase 3 studies in Bardet-Biedl syndrome and Alström syndrome, as well as preparation for regulatory filing for these indications;

- approximately $16 million to expand the clinical development of setmelanotide in new indications, including POMC heterozygous deficiency obesity and POMC epigenetics, as well as development of our once-weekly formulation of setmelanotide;

- approximately $53 million for initiatives to expand the diagnosis of genetic obesity, including genetic sequencing of potential patients from targeted populations, expansion of our GO-ID study and TEMPO registry, research and scientific exchange related to our ongoing genotyping and genetic epidemiology studies; and

- the balance to be used for other activities, including the preclinical development of RM-853 and general corporate purposes.

Our expected use of net proceeds from this offering represents our current intentions based upon our present plans and business condition. As of the date of this prospectus, we cannot predict with certainty all of the particular uses for the net proceeds to be received upon the closing of this offering, or the amounts that we will actually spend on the uses set forth above. The amounts and timing of our actual use of the net proceeds will vary depending on numerous factors, including the progress of our clinical trials and other development efforts for setmelanotide and other factors described in "Risk Factors" beginning on page 15, as well as the amount of cash we use in our operations. As a result, our management will have broad discretion in the application of the net proceeds, and investors will be relying on our judgment regarding the application of the net proceeds of this offering. In addition, we might decide to postpone or not pursue clinical trials or preclinical activities if the net proceeds from this offering and the other sources of cash are less than expected.

Pending application of the net proceeds, we intend to invest the net proceeds from this offering in short- and intermediate-term, interest-bearing obligations, investment-grade instruments, certificates of deposit or direct or guaranteed obligations of the U.S. government. We may still require significant additional capital to fund the continued development of setmelanotide and our operating needs thereafter. We expect to finance our additional cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and licensing arrangements.

MARKET PRICE OF COMMON STOCK

Our common stock has been listed on the Nasdaq Global Market under the symbol "RYTM" since October 5, 2017. Prior to that date, there was no public trading market for our common stock. The following table sets forth for the period indicated the high and low intraday sale price per share of our common stock as reported on the Nasdaq Global Market:

Year Ended December 31, 2017:	High	Low
Fourth Quarter (from October 5, 2017)	$ 33.81	$ 21.38

Year Ended December 31, 2018:	High	Low
First Quarter	$ 32.35	$ 19.25
Second Quarter (through June 15, 2018)	$ 34.99	$ 16.80

The last reported sale price of our common stock on the Nasdaq Global Market on June 15, 2018 was $32.60 per share. As of June 15, 2018, there were 27 holders of record of our common stock. This number does not reflect beneficial owners whose shares are held in street name.

DIVIDEND POLICY

We currently intend to retain all available funds and any future earnings for use in the operation of our business and do not anticipate paying any dividends on our common stock in the foreseeable future. Any future determination to declare dividends will be made at the discretion of our board of directors and will depend on our financial condition, operating results, capital requirements, general business conditions and other factors that our board of directors may deem relevant.

CAPITALIZATION

The following table sets forth our cash and cash equivalents and short-term investments and capitalization as of March 31, 2018, as follows:

- on an actual basis; and
- on an as adjusted basis to give effect to the issuance and sale of $150.0 million of shares of our common stock in this offering at an assumed offering price of $32.60 per share, which was the last reported sale price of our common stock on the Nasdaq Global Market on June 15, 2018, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

Our capitalization following the closing of this offering will be adjusted based on the actual offering price and other terms of the offering determined at pricing. You should read this information in conjunction with our financial statements and the related notes appearing at the end of this prospectus, the "*Management's Discussion and Analysis of Financial Condition and Results of Operations*" section and other financial information contained in this prospectus. You should also read this table together with the information contained in this prospectus, including "*Use of Proceeds*," and the historical financial statements and related notes included elsewhere in this prospectus.

	As of March 31, 2018	
	Actual	As Adjusted
	(unaudited) (in thousands)	
Cash and cash equivalents and short-term investments	$ 136,453	$ 276,713
Stockholders' equity (deficit):		
Common stock, $0.001 par value; 120,000,000 shares authorized, 27,284,140 shares issued and outstanding actual; 31,885,367 shares issued and outstanding as adjusted	27	32
Additional paid-in capital	260,342	400,597
Accumulated deficit	(126,711)	(126,711)
Total stockholders' equity	133,658	273,918
Total capitalization	$ 133,658	$ 273,918

The information above is illustrative only and our capitalization following the completion of this offering will be adjusted based on the actual offering price and other terms of this offering determined at pricing.

A $1.00 increase (decrease) in the assumed offering price of $32.60 per share, which was the last reported sale price of our common stock on the Nasdaq Global Market on June 15, 2018, would increase (decrease) the amount of cash and cash equivalents, additional paid-in capital, total stockholders' equity (deficit) and total capitalization on an as adjusted basis by approximately $4.3 million, assuming the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. Similarly, each increase (decrease) of one million shares offered by us would increase (decrease) cash and cash equivalents, total stockholders' equity (deficit) and total capitalization on an as adjusted basis by approximately $30.6 million, assuming the assumed offering price remains the same, and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. A one million share increase in the number of shares offered by us together with a concomitant $1.00 increase in the assumed offering price of $32.60 per share, which was the last reported sale price of our common stock on the Nasdaq Global Market on June 15, 2018, would increase each of cash and cash equivalents and total stockholders' (deficit) equity by approximately $35.9 million after deducting underwriting discounts and commissions and estimated offering expenses payable by us. Conversely, a one million share decrease in the number of shares offered by us together with a concomitant $1.00 decrease in the assumed offering price of $32.60 per share, which was the last reported sale price of our common stock on the Nasdaq Global Market on June 15, 2018, would decrease each of cash and cash equivalents and total stockholders' (deficit) equity by approximately $34.0 million after deducting underwriting discounts and commissions and estimated offering expenses payable by us. The as adjusted information discussed above is illustrative only and will be adjusted based on the actual offering price and other terms of this offering determined at pricing.

The number of shares of our common stock to be outstanding after this offering excludes:

- 223,544 shares of common stock issued to Takeda, for the acquisition of the worldwide rights to develop and commercialize RM-853 on April 3, 2018;
- 38,150 shares of common stock issued upon the exercise of stock options after March 31, 2018 at a weighted average exercise price of $4.67 per share;
- 2,682,275 shares of common stock reserved for future issuance under our 2017 equity incentive plan, or the 2017 Plan, as of March 31, 2018;
- 272,841 shares of common stock reserved for future issuance under our 2017 employee stock purchase plan, as of March 31, 2018; and
- 2,427,629 shares of common stock issuable upon the exercise of stock options outstanding as of March 31, 2018 under our 2017 equity incentive plan at a weighted average exercise price of $11.85.

DILUTION

If you invest in our common stock in this offering, your ownership interest will be immediately diluted to the extent of the difference between the initial public offering price per share and the as adjusted net tangible book value per share of our common stock after this offering.

Our historical net tangible book value as of March 31, 2018 was approximately $133.7 million, or $4.90 per share of our common share. Our historical net tangible book value represents our total tangible assets less our total liabilities. Net historical tangible book value per common share is our historical net tangible book value divided by the number of common shares outstanding as of March 31, 2018.

Our as adjusted net tangible book value represents our net tangible book value, plus the effect of the issuance and sale of $150.0 million of shares of our common stock in this offering at an assumed public offering price of $32.60 per share, the last reported sale price of our common stock on the Nasdaq Global Market on June 15, 2018, after deducting underwriting discounts and commissions and estimating offering expenses payable by us. Our as adjusted net tangible book value as of March 31, 2018 was approximately $273.9 million, or $8.59 per share of our common stock. This amount represents an immediate increase in the as adjusted net tangible book value of $3.69 per share to existing shareholders and an immediate dilution of $24.01 per share to new investors purchasing shares at an assumed public offering price of $32.60 per share.

The following table illustrates this dilution on a per share basis:

Assumed public offering price per share		$ 32.60
Historical net tangible book value per share as of March 31, 2018	$ 4.90	
Increase per share attributable to new investors	3.69	
As adjusted net tangible book value per share at March 31, 2018 after giving effect to the offering		8.59
Dilution per share to new investors		$ 24.01

A $1.00 increase (decrease) in the assumed public offering price of $32.60 per share, the last reported sale price of our common stock on the Nasdaq Global Market on June 15, 2018, would increase (decrease) the as adjusted net tangible book value per share after this offering by approximately $0.14 per share and the dilution per share to investors participating in this offering by approximately $0.86 per share, assuming that the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same and after deducting the estimated underwriting discounts and commissions and estimated offering costs payable by us.

The following table summarizes, on an as adjusted basis as of March 31, 2018, the total number of shares purchased from us, the total consideration paid, or to be paid, and the average price per share paid, or to be paid, by existing stockholders and by new investors in this offering at an assumed public offering price of $32.60 per share, the last reported sale price of our common stock on the Nasdaq Global Market on June 15, 2018, before deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. As the table below shows, new investors purchasing shares in this offering will pay an average price per share substantially higher than our existing stockholders paid.

	Shares Purchased		Total Consideration		Average Price
	Number	Percentage	Amount (in thousands)	Percentage	Per Share
Existing stockholders	27,284,140	86%	$ 219,571	59%	$ 8.05
New investors	4,601,227	14%	150,000	41%	32.60
Total	31,885,367	100%	$ 369,571	100%	$ 11.59

Except as otherwise indicated, the discussion and tables above assume no exercise of the underwriters' option to purchase additional shares of our common stock in this offering. If the underwriters' option to purchase additional shares is exercised in full:

- the percentage of outstanding common stock held by existing stockholders will be reduced to 84% of the total number of shares of common stock to be outstanding upon completion of this offering; and

- the number of shares of common stock held by investors participating in this offering will be increased to shares, or 16% of the total number of shares of common stock to be outstanding upon completion of this offering.

As of March 31, 2018, an aggregate of 5,109,904 shares of our common stock was reserved for issuance under our amended and restated 2017 equity incentive plan, or the Plan, and an aggregate of 272,841 shares of our common stock was reserved for issuance under our 2017 employee stock purchase plan. Furthermore, we may choose to raise additional capital through the sale of equity or convertible debt securities due to market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. To the extent that any new options are issued under our equity incentive plans or we issue additional shares of common stock or other equity or convertible debt securities in the future, there will be further dilution to investors participating in this offering.

SELECTED FINANCIAL DATA

The following selected statements of operations data for the years ended December 31, 2015, 2016 and 2017 and the balance sheet data as of December 31, 2015, 2016 and 2017 are derived from our audited financial statements appearing elsewhere in this prospectus. The selected statements of operations data for the three months ended March 31, 2017 and 2018 and the balance sheet data as of March 31, 2018 have been derived from our unaudited financial statements included elsewhere in this prospectus. In our opinion, these unaudited financial statements have been prepared on a basis consistent with our audited financial statements and contain all adjustments, consisting only of normal and recurring adjustments, necessary for a fair presentation of such financial data. In our opinion, you should read this data together with our audited financial statements and related notes appearing elsewhere in this prospectus and the information under the caption "*Management's Discussion and Analysis of Financial Condition and Results of Operations*."

Our financial statements for the periods presented include allocations of costs from certain shared functions provided to us by the Relamorelin Company. These allocations were made based on either a specific identification basis or, when specific identification is not practicable, a proportional cost allocation method which allocates expenses based on the percentage of employee time and research and development effort expended on our business as compared to total employee time and research and development effort, and have been included in our financial statements for the periods presented.

The financial statements included in this prospectus may not necessarily reflect our financial position, results of operations and cash flows as if we had operated as an independent company during all of the periods presented. See "*Prospectus Summary—Corporate Background and Distribution*."

Our historical results are not necessarily indicative of our future results, and our operating results for the three-month period ended March 31, 2018 are not necessarily indicative of the results that may be expected for the fiscal year ending December 31, 2018 or any other interim periods or any future year or period.

	Year Ended December 31, 2015	Year Ended December 31, 2016	Year Ended December 31, 2017	Three Months Ended March 31, 2017	Three Months Ended March 31, 2018
	(in thousands, except share and per share data)				
				(unaudited)	
Operating expenses:					
Research and development	$ 7,148	$ 19,594	$ 22,894	$ 4,873	$ 12,286
Selling, general and administrative	3,425	6,311	9,518	1,516	4,715
Total operating expenses	10,573	25,905	32,412	6,389	17,001
Loss from operations	(10,573)	(25,905)	(32,412)	(6,389)	(17,001)
Other income (expense):					
Revaluation of Series A Investor Right/Obligation and Investor Instrument	(500)	—	(1,863)	—	—
Interest income, net	—	33	566	29	542
Total other income (expense):	(500)	33	(1,297)	29	542
Net loss and comprehensive loss	$ (11,073)	$ (25,872)	$ (33,709)	$ (6,360)	$ (16,459)
Net loss attributable to common stockholders	$ (12,000)	$ (29,074)	$ (37,582)	$ (7,526)	$ (16,459)
Net loss attributable to common stockholders per common share, basic and diluted(1)	$ (1.18)	$ (2.85)	$ (2.83)	$ (0.74)	$ (0.60)
Weighted average common shares outstanding, basic and diluted	10,196,292	10,196,292	13,267,960	10,196,292	27,284,140

	December 31, 2015	December 31, 2016	December 31, 2017	March 31, 2018 (unaudited)
				(unaudited)
Balance Sheet Data:				
Cash, cash equivalents and short-term investments	$ 34,869	$ 10,537	$ 148,082	$ 136,453
Working capital	30,218	6,444	143,951	132,835
Total assets	37,275	12,339	151,736	139,443
Convertible preferred stock	40,000	40,000	—	—
Accumulated deficit	(50,671)	(76,543)	(110,252)	(126,711)
Total stockholders' equity (deficit)	$ (7,999)	$ (32,703)	$ 144,788	$ 133,658

(1) See Note 2 within the notes to our financial statements appearing elsewhere in this prospectus for a description of the methods used to calculate basic and diluted net loss per share.

MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

You should read the following discussion and analysis of our financial condition and results of operations together with our financial statements and the related notes and other financial information included elsewhere in this prospectus. Some of the information contained in this discussion and analysis or set forth elsewhere in this prospectus, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those set forth in the "Risk Factors" section of this prospectus, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are a biopharmaceutical company focused on the development and commercialization of therapeutics for the treatment of rare genetic disorders that result in severe, life-threatening metabolic disorders. Our lead product candidate is setmelanotide, a potent, first-in-class melanocortin-4 receptor, or MC4R, agonist peptide for the treatment of rare genetic disorders of obesity. We believe setmelanotide, for which we have exclusive worldwide rights, has the potential to serve as replacement therapy for the treatment of melanocortin-4, or MC4, pathway deficiencies. MC4 pathway deficiencies result in the disruption of satiety signals and energy homeostasis in the body, which, in turn, leads to intense feelings of hunger and to obesity. Our development efforts are initially focused on obesity related to six single gene-related, or monogenic, MC4 pathway deficiencies—pro-opiomelanocortin, or POMC, leptin receptor, or LepR, Bardet-Biedl syndrome, Alström syndrome, POMC heterozygous, and POMC epigenetic disorders—for which there are currently no effective or approved treatments. We believe that the MC4 pathway is a compelling target for treating these genetic disorders because of its critical role in regulating appetite and weight by promoting satiety and weight control, and that peptide therapeutics are uniquely suited for activating this target.

We have demonstrated proof of concept in Phase 2 clinical trials in POMC deficiency obesity, LepR deficiency obesity, Bardet-Biedl syndrome, and Alström syndrome, four genetic disorders of extreme and unrelenting appetite and obesity, in which setmelanotide dramatically reduced both weight and hunger. The U.S. Food and Drug Administration, or the FDA, has acknowledged the importance of these results by giving setmelanotide Breakthrough Therapy designation for the treatment of obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway. The Breakthrough Therapy designation currently covers indications for: POMC deficiency obesity, LepR deficiency obesity, Bardet-Biedl syndrome, and Alström syndrome. Setmelanotide is currently in Phase 3 development for POMC deficiency obesity and LepR deficiency obesity, and we are initiating a combined Phase 3 trial for Bardet-Biedl syndrome and Alström syndrome. We have completed enrollment in the pivotal cohorts for both our POMC deficiency obesity Phase 3 clinical trial and our LepR deficiency obesity Phase 3 clinical trial. We expect to report initial Phase 3 data from these trials in the third quarter of 2019, and subsequently plan to file for regulatory approval for these two indications concurrently. We believe that we have demonstrated proof of concept in our Phase 2 clinical trial in Bardet-Biedl syndrome and in Alström syndrome, and met with the FDA in May 2018, to discuss a combined pivotal Phase 3 clinical trial in these indications. Based on these preliminary discussions with the FDA, we currently plan to initiate this trial and enroll patients in 2018. We have an ongoing Phase 2 clinical trial in POMC heterozygous deficiency obesity and POMC epigenetic disorders. We reported initial, preliminary results in these additional Phase 2 indications in June 2018, and plan to provide a further update for these indications early in 2019. In total, approximately 300 obese subjects and patients have been treated with setmelanotide in previous and ongoing clinical trials in which setmelanotide demonstrated statistically significant weight loss with good tolerability.

We have leveraged skilled experts, consultants, contract research organizations, or CROs, and contractors to manage our clinical operations under the leadership and direction of our management. We expect to expand our infrastructure to manage our clinical, finance and commercial operations with a higher proportion of full-time employees. We have 36 employees. Of these employees, 24 are engaged in research and development activities, 4 are engaged in pre-commercialization activities and 8 are engaged in support administration, including business development and finance. In the near-term, we expect to significantly expand our clinical, commercial and finance personnel, in particular, and will incur increased expenses as a result.

In March 2018 we acquired exclusive, worldwide rights from Takeda Pharmaceutical Company Limited, or Takeda, to develop and commercialize T-3525770 (now "RM-853"). RM-853 is a potent, orally available ghrelin o-acyltransferase, or GOAT, inhibitor currently in preclinical development for Prader-Willi Syndrome, or PWS. PWS is a rare genetic disorder that results in hyperphagia and early-onset, life-threatening obesity, for which there are no approved therapeutic options. We will assume sole responsibility for the global product development and commercialization of RM-853. Takeda received an upfront fee of $4.4 million which we settled in April 2018 with shares of our common stock, and will receive back-end development milestones, and single-digit royalties on future RM-853 sales.

Our operations to date have been limited primarily to conducting research and development activities for setmelanotide. To date, we have not generated any product revenue and have financed our operations primarily through capital contributions from the Predecessor Company, the Relamorelin Company and the LLC entity and the private placement of equity securities to outside investors. On October 10, 2017 we completed our initial public offering, or IPO, of 8,107,500 shares of common stock at an offering price of $17.00 per share, which included the exercise in full by the underwriters of their option to purchase up to 1,057,500 additional shares of common stock. We received gross proceeds of approximately $137.8 million, before deducting underwriting discounts, commissions and offering related transaction costs. In connection with the IPO, our outstanding shares of convertible preferred stock were automatically converted into 17,406,338 shares of common stock. We will not generate revenue from product sales until we successfully complete development and obtain regulatory approval for setmelanotide, which we expect will take a number of years and is subject to significant uncertainty. We expect to continue to fund our operations through the sale of equity, debt financings or other sources. We intend to build our own marketing and commercial sales infrastructure and we may enter into collaborations with other parties for certain markets outside the United States. However, we may be unable to raise additional funds or enter into such other arrangements when needed on favorable terms, or at all. If we fail to raise capital or enter into such other arrangements as, and when, needed, we may have to significantly delay, scale back or discontinue the development or commercialization of setmelanotide.

As of March 31, 2018, we had an accumulated deficit of $126.7 million. Our net losses were $16.5 million and $6.4 million for the three months ended March 31, 2018 and 2017, respectively. We expect to continue to incur significant expenses and increasing operating losses over the foreseeable future. We expect our expenses will increase substantially in connection with our ongoing activities, as we:

- continue to conduct clinical trials for setmelanotide;
- engage contract manufacturing organizations, or CMOs, for the manufacture of setmelanotide for clinical trials;
- seek regulatory approval for setmelanotide;
- expand our clinical and financial operations and build a marketing and commercialization infrastructure; and
- operate as a public company.

As of March 31, 2018, our existing cash and cash equivalents and short-term investments were approximately $136.5 million. We expect that our existing cash and cash equivalents and short-term investments, combined with the proceeds of this offering, will enable us to fund our operating expenses into the second half of 2020.

Corporate Background and Distribution

We are a Delaware corporation organized in February 2013 under the name Rhythm Metabolic, Inc., and as of October 2015, under the name Rhythm Pharmaceuticals, Inc. Prior to our organization and the Corporate Reorganization referred to below, we were part of Rhythm Pharmaceuticals, Inc., a Delaware corporation which was organized in November 2008 and which commenced active operations in 2010. We refer to this corporation as the Predecessor Company.

In March 2013, the Predecessor Company underwent a corporate reorganization, which we refer to as the Corporate Reorganization, pursuant to which all of the outstanding equity securities of the Predecessor Company were exchanged for units of Rhythm Holding Company, LLC, a newly-organized limited liability company, which we refer to as the LLC entity. After the consummation of this exchange and as part of the Corporate Reorganization, the Predecessor Company contributed setmelanotide and the MC4R agonist program to us and distributed to the LLC entity all of the then issued and outstanding shares of our stock. The result of the Corporate Reorganization was that we and the Predecessor Company became wholly-owned subsidiaries of the LLC entity and the two product candidates and related programs that were originally held by the Predecessor Company were separated, with relamorelin and the ghrelin agonist program being retained by the Predecessor Company and setmelanotide and the MC4R agonist program being held by us. We refer to the Predecessor Company after consummation of the Corporate Reorganization as the Relamorelin Company. The Predecessor Company filed the Investigational New Drug Application, or IND, for setmelanotide in October 2011 and conducted the setmelanotide clinical trials up until the Corporate Reorganization, after which all clinical trials have been conducted by us.

In October 2014, the LLC entity granted to Actavis plc, now owned by Allergan, Inc., or Allergan, an exclusive option to acquire the Relamorelin Company. The transaction was limited to the acquisition of the Relamorelin Company and did not include our company. In October 2016, the option to acquire the Relamorelin Company was exercised and the sale to Allergan closed on December 15, 2016.

In January 2017 and August 2017, we sold 20,475,001 shares and 20,474,998 shares, respectively, of our series A convertible preferred stock to certain investors. Following the closing of our series A convertible preferred stock financings, the LLC entity remained our largest stockholder, with the balance of our stock being owned by our series A investors. In August 2017, the LLC entity exchanged 8,578,646 of its shares of our common stock for 78,666,209 newly-issued shares of our series A-1 junior preferred stock and the LLC entity distributed all of its shares of our series A-1 junior preferred stock to the holders of its preferred units and the remaining 1,617,646 shares of our common stock to the holders of its common units. We refer to the exchange and distribution as the Distribution. The series A-1 junior preferred stock converted into shares of our common stock on a 9.17-for-1 basis upon the closing of our IPO. Following the Distribution, the LLC entity did not own any of our common stock.

In connection with our IPO, we effected a 1-for-9.17 reverse stock split of our outstanding common stock on September 29, 2017. All share and per share amounts in the financial statements have been retrospectively adjusted for all periods presented to give effect of the reverse stock split.

Financial Operations Overview

Revenue

To date, we have not generated any revenue from product sales and do not expect to generate any revenue from the sale of setmelanotide for at least several years. We cannot predict if, when, or to what extent we will generate revenues from the commercialization and sale of setmelanotide. Setmelanotide is currently our only product candidate, and we may never succeed in achieving regulatory approval for setmelanotide or any other product candidate that we decide to pursue in the future.

Research and development expenses

Research and development expenses consist primarily of costs incurred for our research activities, including our drug discovery efforts, and the development of setmelanotide, which include:

- expenses incurred under agreements with third parties, including CROs that conduct research and development and preclinical activities on our behalf, and the cost of consultants and CMOs that manufacture drug products for use in our preclinical studies and clinical trials;
- employee-related expenses including salaries, benefits, and stock-based compensation expense;
- the cost of lab supplies and acquiring, developing, and manufacturing preclinical study materials; and
- facilities, depreciation, and other expenses, which include rent and maintenance of facilities, insurance and other operating costs.

We expense research and development costs to operations as incurred. Nonrefundable advance payments for goods or services to be received in the future for use in research and development activities are recorded as prepaid expenses. The capitalized amounts are expensed as the related goods are delivered or the services are performed.

The following table summarizes our current research and development expenses.

Research and development summary	Year Ended December 31, 2015	Year Ended December 31, 2016	Year Ended December 31, 2017	Three Months Ended March 31, 2017	Three Months Ended March 31, 2018
	(in thousands)			(unaudited)	
Research and development expense	$ 7,148	$ 19,594	$ 22,894	$ 4,873	$ 12,286

We are unable to predict the duration and costs of the current or future clinical trials of setmelanotide. The duration, costs, and timing of clinical trials and development of setmelanotide will depend on a variety of factors, including:

- the scope, rate of progress, and expense of our ongoing, as well as any additional, clinical trials and other research and development activities;
- the rate of enrollment in clinical trials;
- the safety and efficacy demonstrated by setmelanotide in future clinical trials;
- changes in regulatory requirements;
- changes in clinical trial design; and
- the timing and receipt of any regulatory approvals.

A change in the outcome of any of these variables with respect to the development of setmelanotide would significantly change the costs and timing associated with its development and potential commercialization.

Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect research and development costs to increase significantly for the foreseeable future as our setmelanotide development program progresses. However, we do not believe that it is possible at this time to accurately project total program-specific expenses to commercialization and there can be no guarantee that we can meet the funding needs associated with these expenses.

Selling, general and administrative expenses

Selling expenses consist of professional fees related to preparation for the eventual commercialization of setmelanotide, if approved, as well as salaries and related benefits for commercial employees, including stock-based compensation. As we accelerate our preparation for commercialization and, if it is approved, start to market setmelanotide and as we explore new collaborations to develop and commercialize setmelanotide, we anticipate that these expenses will materially increase.

General and administrative expenses consist primarily of salaries and other related costs, including stock-based compensation, relating to our full-time employees. Other significant costs include rent, legal fees relating to patent and corporate matters and fees for accounting and consulting services.

The following table summarizes our current selling, general and administrative expenses.

Selling, general and administrative summary	Year Ended December 31, 2015	Year Ended December 31, 2016	Year Ended December 31, 2017	Three Months Ended March 31, 2017	Three Months Ended March 31, 2018
	(in thousands)			(unaudited)	
Selling, general and administrative expense	$ 3,425	$ 6,311	$ 9,518	$ 1,516	$ 4,715

We anticipate that our selling, general and administrative expenses will increase in the future to support continued and expanding development efforts, potential commercialization of setmelanotide and increased costs of operating as a public company. These increases will likely include increased costs related to the hiring of additional personnel and fees to outside consultants, lawyers and accountants, compliance with exchange listing and SEC expenses, insurance and investor relations costs, among other expenses.

Critical Accounting Policies and Estimates

Our discussion and analysis of our financial condition and results of operations are based on our financial statements, which we have prepared in accordance with United States generally accepted accounting principles. The preparation of these financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements, as well as the reported amounts of revenues and expenses during the reporting periods. On an ongoing basis, we evaluate our estimates and judgments, including those described in greater detail below. We base our estimates on historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in the notes to our financial statements included elsewhere in this prospectus, we believe that the following accounting policies are the most critical to aid in fully understanding and evaluating our financial condition and results of operations.

Basis of Presentation

Presentation

We have historically existed and functioned as part of the consolidated businesses of the Predecessor Company. Our MC4 business was contributed to us from the Predecessor Company on March 21, 2013 as part of the Corporate Reorganization. At that time, we also entered into the Payroll Services Agreement. In December 2016, the shared employees terminated their existing employment agreements and entered into new agreements with us. Until December 2016, we shared costs with the Relamorelin Company, including finance, accounting, research and development and operations. These shared costs were allocated to us from the Relamorelin Company for the purposes of preparing the financial statements based on a specific identification basis or, when specific identification is not practicable, a proportional cost allocation method which allocates expenses based upon the percentage of employee time and research and development effort expended on our business as compared to total employee time and research and development effort. The proportional use basis adopted to allocate shared costs is in accordance with the guidance of Staff Accounting Bulletin Topic 1B. Our management has determined that the proportional use method of allocating costs to us from the Relamorelin Company is reasonable.

Accrued research and development expenses

As part of the process of preparing our financial statements, we are required to estimate the value associated with goods and services received in the period in connection with research and development activities. This process involves reviewing quotations and contracts, identifying services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost, or alternatively, the deferral of amounts paid for goods or services to be incurred in the future. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses or prepaid expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us at the time those financial statements are prepared. We periodically confirm the accuracy of our estimates with the service providers and make adjustments if necessary. The significant estimates in our accrued research and development expenses include fees paid to CROs and CMOs in connection with research and development activities.

We accrue our expenses related to CROs and CMOs based on our estimates of the services received and efforts expended pursuant to quotes and contracts with CROs and CMOs that conduct research and development and manufacturing on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. The allocation of CRO upfront expenses for both clinical trials and preclinical studies generally tracks actual work activity. However, there may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the research and development expense. In accruing service fees delivered over a period of time, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust accrued or prepaid expense accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, if our estimates of the status and timing of services performed differ from the actual status and timing of services performed, it could result in us reporting amounts that are too high or too low in any particular period. To date, there have been no material differences between our estimates of such expenses and the amounts actually incurred.

2017 Series A Investor Instrument

Pursuant to the 2017 series A preferred stock purchase agreement, by and among us and certain purchasers, and as part of an initial tranche closing, we issued 20,475,001 shares of series A preferred stock at a purchase price of $1.00 per share in January 2017. The series A preferred stock purchase agreement provided for the delayed issuance by us of up to an additional 20,474,998 shares of series A preferred stock as part of a second tranche closing at a purchase price of $1.00 per share. The series A investors had the obligation, upon notification by us, or the 2017 Series A Investor Right/Obligation, to purchase 20,474,998 additional shares of series A preferred stock as part of a second tranche of financing at such time as: (1) our cash, cash equivalents and short-term investments balance, net of accounts payable and accrued liabilities, falling below $5.0 million and (2) our satisfaction of contractual and customary representations and warranties, or the 2017 Second Tranche Milestone. On August 18, 2017, the series A investors waived the $5.0 million cash balance requirement of the 2017 second tranche milestone and such second tranche financing was consummated. As a result of these two tranches, we issued 40.95 million shares of our series A preferred stock, resulting in aggregate gross proceeds of $40.95 million.

We have classified our 2017 Series A Investor Instrument (See Note 4 to our financial statements included elsewhere in this prospectus) as a liability as it is a free-standing financial instrument. The 2017 Series A Investor Instrument was recorded at fair value upon the issuance of our series A preferred stock in January 2017, and subsequently remeasured to fair value at each reporting period. Changes in fair value of this financial instrument is recognized as a component of other income (expense), net in the statement of operations and comprehensive loss. We estimated the fair value of the 2017 Series A Investor Right/Obligations as the probability-weighted present value of the expected benefit of the investment.

We used the Black-Scholes option-pricing model, which incorporates assumptions and estimates, to value the 2017 Series A Investor Call Option and assessed these assumptions and estimates on a quarterly basis as additional information impacting the assumptions was obtained. Estimates and assumptions impacting the fair value measurement include the fair value per share of the underlying series A preferred stock, the expected term of the 2017 Series A Investor Call Option, risk-free interest rate, expected dividend yield and expected volatility of the price of the underlying preferred stock. We determined the fair value per share of the underlying preferred stock by taking into consideration the most recent sale of our convertible preferred stock and the investors' right to invest in a subsequent tranche. As we were a private company and lacked company-specific historical and implied volatility information of our stock, we estimated our expected stock volatility based on the historical volatility of publicly traded peer companies for a term comparable to the estimated term of the 2017 Series A Investor Call Option. The risk-free interest rate was determined by reference to the U.S. Treasury yield curve for time periods approximately equal to the estimated term of the 2017 Series A Investor Call Option. A dividend yield of zero was assumed. The fair value of the Series A Investor Instrument is determined to be the sum of the fair values of the 2017 Series A Investor Right/Obligation and the 2017 Investor Call Option.

Stock-based compensation

In August 2015, our Board of Directors and our stockholders approved and we adopted the 2015 equity incentive plan, as amended and in effect prior to the closing of our IPO, or the 2015 Plan, which we terminated upon consummation of our IPO and replaced with the 2017 equity incentive plan, or the 2017 Plan. The 2017 Plan provides for the grant of incentive and non-qualified stock options and restricted stock and stock grants to employees, consultants, advisors and directors, as determined by the Board of Directors. We have reserved 5,109,904 shares of common stock under the 2017 Plan. The first option grants issued by us under the 2015 Plan were issued in the fourth quarter of 2015. Shares of common stock issued upon exercise of stock options are generally issued from authorized but unissued shares. The 2017 Plan provides that the exercise price of incentive stock options cannot be less than 100% of the fair market value of the common stock on the date of the award for participants who own less than 10% of the total combined voting power of stock, and not less than 110% for participants who own more than 10% of the voting power. Options and restricted stock granted under the 2017 Plan will vest over periods as determined by our Compensation Committee and approved by our Board of Directors.

We estimate the fair value of our stock-based awards to employees and non-employees using the Black-Scholes option-pricing model, which requires the input of highly subjective assumptions, including (a) the expected volatility of our stock, (b) the expected term of the award, (c) the risk-free interest rate, and (d) expected dividends. Previously due to the lack of a public market for the trading of our common stock and a lack of company-specific historical and implied volatility data, we have based our estimate of expected volatility on the historical volatility of a group of companies in the pharmaceutical and biotechnology industries in a similar stage of development as us and that are publicly traded. For these analyses, we have selected companies with comparable characteristics to ours including enterprise value, risk profiles and with historical share price information sufficient to meet the expected life of the stock-based awards. We compute the historical volatility data using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of our stock-based awards. We will continue to apply this process until a sufficient amount of historical information regarding the volatility of our own stock price becomes available. We have estimated the expected life of our employee stock options using the "simplified" method, whereby, the expected life equals the average of the vesting term and the original contractual term of the option. The risk-free interest rates for periods within the expected life of the option are based on the U.S. Treasury yield curve in effect during the period the options were granted. Upon adopting ASU 2016-09, *Improvements to Employee Share-Based Payment Accounting (Topic 718)* on January 1, 2017, we have elected to account for forfeitures as they occur.

Income taxes

Income taxes have been calculated on a separate tax return basis. Certain of our activities and costs have been included in the tax returns filed by the Relamorelin Company and the LLC entity. Prior to the Corporate Reorganization, our operations were included in the tax returns filed by the Predecessor Company. We have filed tax returns on our own behalf since the Corporate Reorganization.

We account for uncertain tax positions in accordance with the provisions of Accounting Standards Codification, or ASC, Topic 740, *Accounting for Income Taxes*, or ASC 740. When uncertain tax positions exist, we recognize the tax benefit of tax positions to the extent that the benefit will more likely than not be realized. The determination as to whether the tax benefit will more likely than not be realized is based upon the technical merits of the tax position as well as consideration of the available facts and circumstances. As of December 31, 2017, we do not have any uncertain tax positions.

Income taxes are recorded in accordance with ASC 740, which provides for deferred taxes using an asset and liability approach. We recognize deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the financial statements or tax returns. We determine our deferred tax assets and liabilities based on differences between financial reporting and tax bases of assets and liabilities, which are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. Valuation allowances are provided, if based upon the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized.

As of December 31, 2017, we had net operating loss carryforwards to reduce federal and state incomes taxes of approximately $73.1 million and $3.8 million, respectively. If not utilized, these carryforwards begin to expire in 2033. At December 31, 2017, we also had available research and development tax credits for federal and state income tax purposes of approximately $1.9 million and $0.5 million, respectively. The federal and state credits begin to expire in 2033 and 2028, respectively. Additionally, as of December 31, 2017, we had a federal orphan drug credits related to qualifying research of $2.3 million. These tax credit carryforwards begin to expire in 2033 for federal purposes and 2028 for state purposes.

Utilization of the net operating loss and tax credit carryforwards may be subject to a substantial annual limitation due to ownership change limitations that have occurred previously or that could occur in the future, as provided by Section 382 of the Code, or Section 382, as well as similar state provisions and other provisions of the Code. Ownership changes may limit the amount of net operating losses and tax credit carryforwards that can be utilized annually to offset future taxable income and tax, respectively. In general, an ownership change, as defined by Section 382, results from transactions that increase the ownership of 5.0% stockholders in the stock of a corporation by more than 50% in the aggregate over a three-year period.

Results of Operations

Comparison of three months ended March 31, 2018 and 2017

The following table summarizes our results of operations for the three months ended March 31, 2018 and 2017, together with the changes in those items in dollars and as a percentage:

	Three Months Ended March 31,		Change	
	2018	2017	$	%
	(in thousands) (unaudited)			
Statement of Operations Data:				
Operating Expenses:				
Research and development	$ 12,286	$ 4,873	$ 7,413	152%
Selling, general, and administrative	4,715	1,516	3,199	211%
Total operating expenses	17,001	6,389	10,612	166%
Loss from operations	(17,001)	(6,389)	(10,612)	166%
Other (expense) income, net	542	29	513	NM%
Net loss and comprehensive loss	$ (16,459)	$ (6,360)	$ (10,099)	159%

Research and development expense. Research and development expense increased by $7.4 million to $12.3 million in 2018 from $4.9 million in 2017, an increase of 152%. The increase was primarily due to the non-cash expense related to the license acquired from Takeda for RM-853, a $1.0 million milestone expense associated with the license agreement with Ipsen and the hiring of additional clinical and development personnel during the second half of 2017.

Selling, general and administrative expense. Selling, general and administrative expense increased by $3.2 million to $4.7 million in 2018 from $1.5 million in 2017, an increase of 211%. The increase was primarily due to increased headcount, the development and building of our commercial organization to drive patient identification, as well as increased professional and consulting fees associated with being a public company.

Comparison of years ended December 31, 2017 and 2016

The following table summarizes our results of operations for the years ended December 31, 2017 and 2016, together with the changes in those items in dollars and as a percentage:

	Year Ended December 31,		Change	
	2017	2016	$	%
	(in thousands)			
Statement of Operations Data:				
Operating Expenses:				
Research and development	$ 22,894	$ 19,594	$ 3,300	17%
Selling, general, and administrative	9,518	6,311	3,207	51%
Total operating expenses	32,412	25,905	6,507	25%
Loss from operations	(32,412)	(25,905)	(6,507)	25%
Other income (loss)	(1,297)	33	(1,330)	NM%
Net loss and comprehensive loss	$ (33,709)	$ (25,872)	$ (7,837)	30%

Research and development expense. Research and development expense increased by $3.3 million to $22.9 million in 2017 from $19.6 million in 2016, an increase of 17%. The increase was primarily due to the increased enrollment for our Phase 3 POMC deficiency obesity trial and preparing for our Phase 3 LepR deficiency obesity trial, as well as the initiation of additional new clinical trials in 2017 and other development activities associated with setmelanotide. We hired additional personnel in the clinical operations department at the end of 2016 and throughout 2017.

Selling, General and administrative expense. Selling, general and administrative expense increased by $3.2 million to $9.5 million in 2017 from $6.3 million in 2016, an increase of 51%. The increase was primarily due to an increase in headcount in both the commercial department and general and administrative departments as well as increased professional and consulting fees associated with being a public company. In 2017, we began the initiation of pre-commercial activities related to setmelanotide.

Comparison of years ended December 31, 2016 and December 31, 2015

The following table summarizes our results of operations for the years ended December 31, 2016 and 2015, together with the changes in those items in dollars and as a percentage:

	Year Ended December 31, 2016	Year Ended December 31, 2015	Change $	Change %
	(in thousands)			
Statement of Operations Data:				
Operating Expenses:				
Research and development	$ 19,594	$ 7,148	$ 12,446	174%
General, and administrative	6,311	3,425	2,886	84%
Total operating expenses	25,905	10,573	15,332	145%
Loss from operations	(25,905)	(10,573)	(15,332)	(145)%
Other income (loss)	33	(500)	533	107%
Net loss and comprehensive loss	$ (25,872)	$ (11,073)	$ (14,799)	(134)%

Research and development expense. Research and development expense increased by $12.4 million to $19.6 million in 2016 from $7.1 million in 2015, an increase of 174%. The increase was partially due to non-cash expenses in 2016 of $0.5 million in stock compensation. Our research and development costs increased subsequent to the initial series A financing at the end of fiscal year 2015 due to the initiation of additional new clinical trials and additional development activities for setmelanotide and the hiring of additional personnel in the clinical operations department in the fourth quarter of 2015 and in 2016, as well as an increase in the overall proportion of research and development expenses allocated to us in 2016.

General and administrative expense. General and administrative expense increased by $2.9 million to $6.3 million in 2016 from $3.4 million in 2015, an increase of 84%. The increase in general and administrative expense was primarily attributable to the write down of capitalized deferred issuance cost of $1.8 million in 2016, as well as an increase in the overall proportion of general and administrative expenses allocated to us in 2016.

Liquidity and Capital Resources

As of March 31, 2018, our existing cash and cash equivalents and short-term investments were approximately $136.5 million.

Cash flows

The following table provides information regarding our cash flows for the years ended December 31, 2017, 2016, and 2015 and the three months ended March 31, 2018 and 2017:

	Year Ended December 31,			Three Months Ended March 31,	
	2017	2016	2015	2018	2017
			(in thousands)	(unaudited)	
Net cash provided by (used in):					
Operating activities	$ (29,460)	$ (23,219)	$ (6,752)	$ (11,651)	$ (7,016)
Investing activities	(110,044)	(5,110)	(17)	20,607	(8,019)
Financing activities	167,200	—	41,711	—	20,377
Net increase (decrease) in cash, cash equivalents and restricted cash	$ 27,696	(28,329)	34,942	8,956	5,342

Net cash used in operating activities

The use of cash in all periods resulted primarily from our net losses adjusted for non-cash charges and changes in components of working capital.

Net cash used in operating activities was $29.5 million for the year ended December 31, 2017, and consisted primarily of a net loss of $29.3 million adjusted for non-cash items, which were comprised of stock-based compensation, depreciation and amortization and the mark to market revaluation of the 2017 Series A Investor Instrument. The significant items in the change in operating assets and liabilities include an increase in accounts payable, accrued expenses and other current liabilities of $1.9 million offset by an increase of approximately $1.9 million in prepaid expenses and other current assets.

Net cash used in operating activities was $23.2 million for the year ended December 31, 2016, and consisted primarily of a net loss of $24.5 million adjusted for non-cash items, which consisted of stock-based compensation, depreciation and amortization and deferred rent expense. The significant items in the change in operating assets and liabilities include a decrease of $1.5 million in deferred issuance costs offset by a decrease in deferred grant income of approximately $0.3 million.

Net cash used in operating activities was $7.0 million for the year ended December 31, 2015, and consisted primarily of a net loss of $9.4 million adjusted for non-cash items, which were comprised of stock-based compensation, warrant amendment expense and mark to market revaluation of the 2015 Series A Investor Right/Obligation. The significant items in the change in operating assets and liabilities include an increase in accounts payable, accrued expenses and other current liabilities of $4.7 million offset by an increase of approximately $2.1 million in deferred issuance costs and prepaid expenses and other current assets.

Net cash used in operating activities was $11.7 million for the three months ended March 31, 2018 and consisted primarily of a net loss of $11.0 million adjusted for non-cash items, which consisted of the non-cash research and development license expense for RM-853, stock-based compensation, depreciation and amortization and deferred rent expense. The change in operating assets and liabilities reflected a total use of cash of approximately $0.7 million mainly for a decrease in accrued expenses and prepaid expenses.

Net cash used in operating activities was $7.0 million for the three months ended March 31, 2017, and consisted primarily of a net loss of $6.1 million adjusted for non-cash items, which consisted of stock-based compensation, depreciation and amortization and deferred rent expense. The significant items in the change in operating assets and liabilities include a decrease in accounts payable of $0.5 million and an increase in prepaid clinical trial expenses of approximately $0.3 million.

Net cash used in investing activities

Net cash used in investing activities for the year ended December 31, 2017 relates to the net purchases of short-term investments of $110.0 million.

Net cash used in investing activities for the year ended December 31, 2016 relates to the net purchases of short-term investments of $4.1 million and the buildout of our offices and furniture and equipment of $1.1 million.

Net cash used in investing activities for the year ended December 31, 2015 relates to our design costs incurred related to our new facility lease.

Net cash provided by investing activities for the three months ended March 31, 2018 relates to the net maturities of short-term investments of $20.6 million.

Net cash used in investing activities for the three months ended March 31, 2017 relates to the net purchases of short-term investments of $8.0 million.

Net cash provided by financing activities

Net cash provided by financing activities was $167.2 million for the year ended December 31, 2017, which represents the net proceeds of $40.8 million from the 2017 issuance of series A preferred stock and the net proceeds of $125.7 million from our IPO in October 2017.

Net cash provided by financing activities was $41.7 million for the year ended December 31, 2015, consisting of $39.6 million of net proceeds from the issuance of series A preferred stock and an equity contribution of $2.1 million from the LLC entity.

Net cash provided by financing activities was $20.4 million for the three months ended March 31, 2017, which represents the net proceeds from the first tranche of our issuance of series A preferred stock in January 2017.

Funding requirements

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the clinical development of and seek marketing approval for setmelanotide. In addition, if we obtain marketing approval for setmelanotide, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution to the extent that such sales, marketing and distribution are not the responsibility of potential collaborators. We also expect to incur additional costs associated with operating as a public company.

We expect that our existing cash and cash equivalents and the proceeds of this offering will enable us to fund our operating expenses into the second half of 2020. We may need to obtain substantial additional funding in connection with our research and development activities and any continuing operations thereafter. If we are unable to raise capital when needed or on favorable terms, we would be forced to delay, reduce or eliminate our research and development programs or future commercialization efforts.

Our future capital requirements will depend on many factors, including:

- the scope, progress, results and costs of clinical trials for our setmelanotide program;

- the costs, timing and outcome of regulatory review of our setmelanotide program;

- the obligations owed to Ipsen Pharma S.A.S., or Ipsen, Camurus AB, or Camurus, and Takeda, pursuant to our license agreements;
- the extent to which we acquire or in-license other product candidates and technologies;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims; and
- our ability to establish and maintain additional collaborations on favorable terms, if at all.

Developing our setmelanotide program is a time-consuming, expensive and uncertain process that may take years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve product sales. In addition, setmelanotide, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of setmelanotide that we do not expect to be commercially available for several years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and licensing arrangements. In August 2015, December 2015, January 2017 and August 2017, respectively, we issued 25,000,000, 15,000,000, 20,475,001 and 20,474,998, shares of series A preferred stock, respectively, at a price of $1.00 per share, resulting in gross proceeds of $81.0 million. In October 2017 we completed our IPO in which we received net proceeds of $125.7 million.

To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing, if available, involves agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

If we raise funds through additional collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our setmelanotide program on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market our setmelanotide program that we would otherwise prefer to develop and market ourselves.

Contractual obligations

We enter into agreements in the normal course of business with CROs and CMOs for clinical trials and clinical supply manufacturing and with vendors for clinical research studies and other services and products for operating purposes. We do not classify these as contractual obligations where the contracts are cancelable at any time by us, generally upon 30 days' prior written notice to the vendor.

Milestone and royalty payments associated with our license agreements with Ipsen, Camurus and Takeda, have not been included as contractual obligations as we cannot reasonably estimate if or when they will occur. Under the terms of the Ipsen license agreement, assuming that setmelanotide is successfully developed, receives regulatory approval and is commercialized, Ipsen may receive aggregate payments of up to $40.0 million upon the achievement of certain development and commercial milestones under the license agreement and royalties on future product sales. The majority of the aggregate payments under the Ipsen license agreement are for milestones that may be achieved no earlier than first commercial sale of setmelanotide. In the event that we enter into a sublicense agreement, we will make payments to Ipsen, depending on the date of the sublicense agreement, ranging from 10% to 20% of all revenues actually received under the sublicense agreement. Under the terms of the Camurus license agreement, assuming that setmelanotide is successfully developed, receives regulatory approval and is commercialized, Camurus may receive aggregate payments of up to $64.75 million upon the achievement of certain development and commercial milestones under the license agreement and royalties on future product sales. The majority of the aggregate payments under the Camurus license agreement are for milestones that may be achieved no earlier than first commercial sale of this formulation of setmelanotide. Under the terms of the Takeda license agreement, assuming that RM-853, is successfully developed, receives regulatory approval and is commercialized, Takeda may receive aggregate payments of up to $140.0 million upon the achievement of certain development and commercial milestones under the license agreement and royalties on future product sales. The majority of the aggregate payments under the Takeda license agreement are for milestones that may be achieved no earlier than first commercial sale of the RM-853.

In November 2015, we entered into a Lease Agreement for an office facility at 500 Boylston Street, Boston, Massachusetts. The lease term commenced in May 2016 and has a term of five years with a five-year renewal option to extend the lease.

Future minimum payments under the Lease Agreement as of December 31 2017, are as follows:

	Operating Lease
2018	$ 298
2019	305
2020	311
2021	131
Total	$ 1,045

Off-balance Sheet Arrangements

We did not have, during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined under applicable SEC rules.

Quantitative and Qualitative Disclosures about Market Risk

We are exposed to market risk related to changes in interest rates. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our investments, including cash equivalents, are in the form, or may be in the form of, money market funds or marketable securities and are or may be invested in U.S. Treasury and U.S. government agency obligations. Due to the short-term maturities and low risk profiles of our investments, an immediate 100 basis point change in interest rates would not have a material effect on the fair market value of our investments.

We are not materially exposed to market risk related to changes in foreign currency exchange rates.

JOBS Act

In April 2012, the JOBS Act was enacted. Section 107 of the JOBS Act provides that an "emerging growth company," or EGC, can take advantage of the extended transition period provided in Section 7(a)(2)(B) of the Securities Act for complying with new or revised accounting standards. Thus, an EGC can delay the adoption of certain newly implemented accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this extended transition period and, as a result, we will adopt new or revised accounting standards on the relevant dates on which adoption of such standards is required for other public companies.

We are in the process of evaluating the benefits of relying on other exemptions and reduced reporting requirements under the JOBS Act. Subject to certain conditions, as an EGC, we intend to rely on certain of these exemptions, including without limitation, (i) providing an auditor's attestation report on our system of internal controls over financial reporting pursuant to Section 404(b) of the Sarbanes-Oxley Act and (ii) complying with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements, known as the auditor discussion and analysis. We will remain an emerging growth company until the earlier of (1) December 31, 2022, and (2) the last day of the fiscal year (a) in which we have total annual gross revenue of at least $1.07 billion, or (b) in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeds $700 million as of the prior June 30th, and (3) the date on which we have issued more than $1.0 billion in non-convertible debt during the prior three year period.

BUSINESS

Overview

We are a biopharmaceutical company focused on the development and commercialization of therapeutics for the treatment of rare genetic disorders that result in severe, life-threatening metabolic disorders. Our lead product candidate is setmelanotide, a potent, first-in-class melanocortin-4 receptor, or MC4R, agonist peptide for the treatment of rare genetic disorders of obesity. We believe setmelanotide, for which we have exclusive worldwide rights, has the potential to serve as replacement therapy for the treatment of melanocortin-4, or MC4, pathway deficiencies. MC4 pathway deficiencies result in the disruption of satiety signals and energy homeostasis in the body, which, in turn, leads to intense feelings of hunger and to obesity. Our development efforts are initially focused on obesity related to six single gene-related, or monogenic, MC4 pathway deficiencies—pro-opiomelanocortin, or POMC, leptin receptor, or LepR, Bardet-Biedl syndrome, Alström syndrome, POMC heterozygous, and POMC epigenetic disorders—for which there are currently no effective or approved treatments. We believe that the MC4 pathway is a compelling target for treating these genetic disorders because of its critical role in regulating appetite and weight by promoting satiety and weight control, and that peptide therapeutics are uniquely suited for activating this target.

We have demonstrated proof of concept in Phase 2 clinical trials in POMC deficiency obesity, LepR deficiency obesity, Bardet-Biedl syndrome, and Alström syndrome, four genetic disorders of extreme and unrelenting appetite and obesity, in which setmelanotide dramatically reduced both weight and hunger. The U.S. Food and Drug Administration, or the FDA, has acknowledged the importance of these results by giving setmelanotide Breakthrough Therapy designation for the treatment of obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway. The Breakthrough Therapy designation currently covers indications for: POMC deficiency obesity, LepR deficiency obesity, Bardet-Biedl syndrome, and Alström syndrome. Setmelanotide is currently in Phase 3 development for POMC deficiency obesity and LepR deficiency obesity, and we are initiating a combined Phase 3 trial for Bardet-Biedl syndrome and Alström syndrome. We have completed enrollment in the pivotal cohorts for both our POMC deficiency obesity Phase 3 clinical trial and our LepR deficiency obesity Phase 3 clinical trial. We expect to report initial Phase 3 data from these trials in the third quarter of 2019, and subsequently plan to file for regulatory approval for these two indications concurrently. We believe that we have demonstrated proof of concept in our Phase 2 clinical trial in Bardet-Biedl syndrome and in Alström syndrome, and met with the FDA in May 2018, to discuss a combined pivotal Phase 3 clinical trial in these indications. Based on these preliminary discussions with the FDA, we currently plan to initiate this trial and enroll patients in 2018. We have an ongoing Phase 2 clinical trial in POMC heterozygous deficiency obesity and POMC epigenetic disorders. We reported initial, preliminary results in these additional Phase 2 indications in June 2018, and plan to provide a further update for these indications early in 2019. In total, approximately 300 obese subjects and patients have been treated with setmelanotide in previous and ongoing clinical trials in which setmelanotide demonstrated statistically significant weight loss with good tolerability.

Obesity is epidemic in the United States and current treatment approaches have demonstrated limited long-term success for most obese patients. We are taking a different approach to obesity drug development by leveraging new understanding of the genetic causes of severe obesity to develop innovative therapies that we believe have the potential for compelling efficacy. Setmelanotide's unique mechanism of action at MC4R enables a targeted approach to treating very severe obesity in patients with specific, monogenic defects in the MC4 signaling pathway. By restoring impaired function in this pathway, setmelanotide can serve as replacement therapy for genetic deficiencies, with the potential for dramatic improvements in weight and appetite. We believe we are at the forefront of developing a therapeutic option to improve treatment outcomes in subtypes of severe obesity caused by genetically-defined defects in the MC4 pathway.

Setmelanotide activates MC4R, which is part of the key pathway that can independently regulate energy homeostasis, which refers to the body's energy balance, and appetite. The critical role of the MC4 pathway in weight regulation was validated with the discovery that single genetic defects along this pathway result in early onset and severe obesity. An expanding set of severe obesity genetic defects are now identified that involve genes in the pathway which are either upstream of MC4R—for example POMC deficiency obesity and LepR deficiency obesity—or genes that are downstream of MC4R or affect MC4R itself. We are focusing setmelanotide clinical development on patients with monogenic upstream genetic defects in which obesity is life-threatening but the downstream MC4 pathway is fully functional. We believe setmelanotide has the potential to restore lost activity in the MC4 pathway by bypassing the defects upstream of MC4R, and activating the MC4 pathway below such defects. In this way, setmelanotide may serve as replacement therapy to reestablish weight and appetite control in patients with these genetic disorders.

The first generation of MC4R agonists were predominantly small molecules that failed in clinical trials due to safety issues, particularly increases in blood pressure, in addition to having limited efficacy. In contrast, setmelanotide, a novel eight amino acid peptide, retains the specificity and functionality of the naturally occurring hormone that activates MC4R, and has exhibited preliminary evidence of efficacy without adversely affecting blood pressure in our Phase 1 and ongoing Phase 2 clinical trials. We are currently evaluating setmelanotide, which is administered by subcutaneous, or SC, injection, for the treatment of six genetic disorders of obesity: POMC deficiency obesity, LepR deficiency obesity, Bardet-Biedl syndrome, Alström syndrome, POMC heterozygous deficiency obesity, and POMC epigenetic disorders. We have positive Phase 2, proof of concept results for four of these indications thus far—POMC deficiency obesity, LepR deficiency obesity, both of which are currently in Phase 3 development—and Bardet-Biedl syndrome and Alström syndrome, for which we currently plan to initiate a combined Phase 3 clinical trial, and enroll patients, in 2018.

POMC deficiency obesity is a life-threatening, ultra-rare orphan disease, with approximately 50 patients reported to date. Ultra-rare orphan diseases are generally categorized as those that affect fewer than 20 patients per million. We estimate that our addressable patient population for this disorder is approximately 100 to 500 patients in the United States. Patients with POMC deficiency have unrelenting hunger, or hyperphagia, that begins in infancy and they develop severe, early onset obesity. POMC deficiency obesity results from two different homozygous genetic defects, both upstream of MC4R, that result in loss of function in the MC4 pathway. Currently, there is no approved treatment for the obesity and hyperphagia associated with this genetic disorder. We have completed enrollment of the pivotal cohort in our Phase 3 open label, single arm, multinational trial to evaluate the safety and efficacy of setmelanotide for POMC deficiency obesity, with setmelanotide administered once daily by subcutaneous, or SC, injection for 12 months, and we plan to report initial Phase 3 data in the third quarter of 2019. Previously, we completed a positive Phase 2 clinical trial in which two patients were enrolled and received treatment. These results were published in the New England Journal of Medicine in July 2016. The first patient in this trial lost 146.6 lbs. over 118 weeks, from a baseline weight of 341.7 lbs., and the second patient lost 89.3 lbs. over 64 weeks, from a baseline weight of 336.9 lbs. Both patients experienced substantial reductions in hunger, with hunger scores falling to one to two from baseline scores of nine to 10. Hunger scores were measured using a Likert score of zero to 10, where zero represents no hunger and 10 represents extreme hunger. Setmelanotide was generally well tolerated in this Phase 2 trial.

LepR deficiency obesity is an ultra-rare orphan disease that results in hyperphagia and severe early-onset obesity, with an estimated prevalence of 1% of subjects with severe, early-onset obesity. We estimate that our addressable patient population for this disorder is approximately 500 to 2,000 patients in the United States. Like other deficiencies upstream in the MC4 pathway, LepR deficiency results in loss of function in the MC4 pathway. Therefore, patients with this indication also manifest hyperphagia and severe obesity from early childhood. Currently, there is no approved treatment for the obesity and hyperphagia associated with LepR deficiency obesity. We have completed enrollment of the pivotal cohort in our Phase 3 open label, single arm, multinational trial to evaluate the safety and efficacy of setmelanotide for LepR deficiency obesity, with setmelanotide administered once daily by SC injection for 12 months, and we plan to report initial Phase 3 data in the third quarter of 2019. Previously, we completed a positive Phase 2 clinical trial in which three patients were enrolled and received treatment in this trial each experiencing significant weight loss and substantial reductions in hunger. These results were published in Nature Medicine in May 2018. Setmelanotide was generally well tolerated in this Phase 2 trial.

Based on our POMC deficiency obesity and LepR deficiency obesity Phase 2 results, the FDA granted setmelanotide Breakthrough Therapy designation for the treatment of obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway, which includes both POMC deficiency obesity and LepR deficiency obesity, enabling an expedited path to approval of setmelanotide for these two indications. The FDA has granted orphan drug designation for setmelanotide for the treatment of POMC deficiency obesity and LepR deficiency obesity.

Bardet-Biedl syndrome is a life-threatening, ultra-rare orphan disease with a prevalence of approximately one in 100,000 in North America. We estimate that our addressable patient population for Bardet-Biedl syndrome obesity is approximately 1,500 to 2,500 patients in the United States. Bardet-Biedl syndrome is a monogenic disorder that causes severe obesity and hyperphagia as well as vision loss, polydactyly, kidney abnormalities, and other signs and symptoms. Currently there are no approved or effective therapies for Bardet-Biedl syndrome. We have demonstrated proof of concept based on data from five patients in our Phase 2 clinical trial in Bardet-Biedl syndrome, indicating that this is also a setmelanotide-responsive, upstream MC4 pathway disorder. Four of these five patients showed early, but significant weight loss and all five patients showed clear improvements in every hunger assessment. We reported preliminary Phase 2 results in the fourth quarter of 2017, and provided an update on these patients in the second quarter of 2018. Based on these results, the FDA recently included Bardet-Biedl syndrome under our existing Breakthrough Therapy designation for setmelanotide. Setmelanotide has been generally well tolerated in this trial.

Alström syndrome is a life-threatening, ultra-rare orphan disease with a prevalence of approximately one in one million in North America. We estimate that our addressable patient population for Alström syndrome is approximately 500 to 1,000 patients worldwide. Alström syndrome is a monogenic disorder, closely related to Bardet-Biedl syndrome, that causes childhood obesity and hyperphagia as well as progressive vision loss, deafness, cardiomegaly, insulin resistance and other signs and symptoms. Currently there are no approved or effective therapies for Alström syndrome. We believe we have recently demonstrated proof of concept in our Phase 2 clinical trial in Alström syndrome, indicating that this is also a setmelanotide responsive, upstream MC4 pathway disorder. Based on these results, the FDA recently included Alström syndrome in our existing Breakthrough Therapy designation for setmelanotide. Setmelanotide has so far been generally well tolerated in this trial.

We met with the FDA in May 2018 to discuss a combined pivotal Phase 3 clinical trial in both Bardet-Biedl syndrome and Alström syndrome. Based on these preliminary discussions with the FDA, we currently plan to initiate this trial and enroll patients in 2018.

We are also focusing on additional monogenic, upstream MC4 pathway deficiencies for which setmelanotide can function as replacement therapy and provide activation of the pathway downstream of the defect, promoting satiety and weight control. We have enrolled patients in Phase 2 proof of concept trials for POMC epigenetic disorders, and for POMC heterozygous deficiency obesity, for which we estimate our addressable population is approximately 4,000 patients in the United States. For all of these patients, hyperphagia and obesity can have significant health consequences for which there is currently no approved treatment. We reported initial, preliminary results from these trials in June 2018, and plan to provide a further update for these indications early in 2019.

In addition to our development of setmelanotide, in April 2018, we announced that we had acquired exclusive, worldwide rights from Takeda Pharmaceutical Company Limited, or Takeda, to develop and commercialize T-3525770, now called RM-853. RM-853 is a potent, orally available ghrelin o-acyltransferase, or GOAT, inhibitor currently in preclinical development for Prader-Willi Syndrome, or PWS. PWS is a rare genetic disorder that results in hyperphagia and early-onset, life-threatening obesity, for which there are no approved therapeutic options. RM-853 is currently in pre-clinical development. We anticipate filing an Investigational New Drug application, or IND, for RM-853 with the FDA in 2020.

Our company was founded in November 2008 by former biopharmaceutical executives who have successfully developed, commercialized and in-licensed innovative pharmaceutical products, and we have subsequently expanded our senior management team to further broaden our team's experience in developing, registering and commercializing new drugs. In addition, our scientific advisory board, or SAB, members have extensive clinical expertise in obesity, endocrinology and metabolic diseases. We intend to leverage the experience of our senior management team and SAB to develop and commercialize setmelanotide. Through our senior management team's network of industry contacts, we will continue to evaluate additional product candidate licensing and acquisition opportunities.

Our setmelanotide patent portfolio includes composition of matter patents for setmelanotide that expire in the United States in 2027, with possible patent term extension to 2032 under the Hatch-Waxman Act. Additional patent coverage may be provided due to pending formulation patent applications, if such pending formulation applications were issued.

Our Strategy

Our goal is to be a leader in developing and commercializing targeted therapies for genetic deficiencies that result in life-threatening metabolic disorders. The key components of our strategy are:

- **Rapidly develop setmelanotide for rare genetic disorders of obesity caused by MC4 pathway deficiencies.** We are aiming to dramatically improve patient outcomes in severe obesity by targeting setmelanotide's mechanism of action to the treatment of patients with genetically-defined defects in the MC4 pathway. We are focusing setmelanotide clinical development on monogenic upstream genetic defects in which obesity is life-threatening but where the downstream MC4 pathway is fully functional. We believe that focusing on these rare life-threatening conditions enables us to rapidly develop and commercialize setmelanotide using relatively small clinical trials.

- **Advance setmelanotide for POMC deficiency obesity and LepR deficiency obesity as our first indications in upstream MC4 pathway deficiencies.** We are currently evaluating setmelanotide for the treatment of six genetic disorders of obesity: POMC deficiency obesity, LepR deficiency obesity, Bardet-Biedl syndrome, Alström syndrome, POMC heterozygous deficiency obesity, and POMC epigenetic disorders. We have completed enrollment of the pivotal cohorts in our Phase 3 trials in POMC deficiency obesity and LepR deficiency obesity, and plan to report initial data from these trials in the third quarter of 2019. We are working with the FDA, based on our Breakthrough Therapy designation, to prepare concurrent New Drug Application, or NDA, filings for these two indications as part of an expedited path to approval for POMC deficiency obesity and LepR deficiency obesity.

- **Advance setmelanotide for Bardet-Biedl syndrome and Alström syndrome as our second set of indications in upstream MC4 pathway deficiencies.** We have demonstrated proof of concept in Bardet-Biedl syndrome and Alström syndrome, indicating that these are also setmelanotide responsive, upstream MC4 pathway disorders. Based on these results, the FDA recently included these disorders under our existing Breakthrough Therapy designation for setmelanotide. In May 2018, we met with the FDA to discuss a combined pivotal Phase 3 clinical trial in both Bardet-Biedl syndrome and Alström syndrome. Based on these preliminary discussions with the FDA, we currently plan to initiate this trial and enroll patients in 2018.

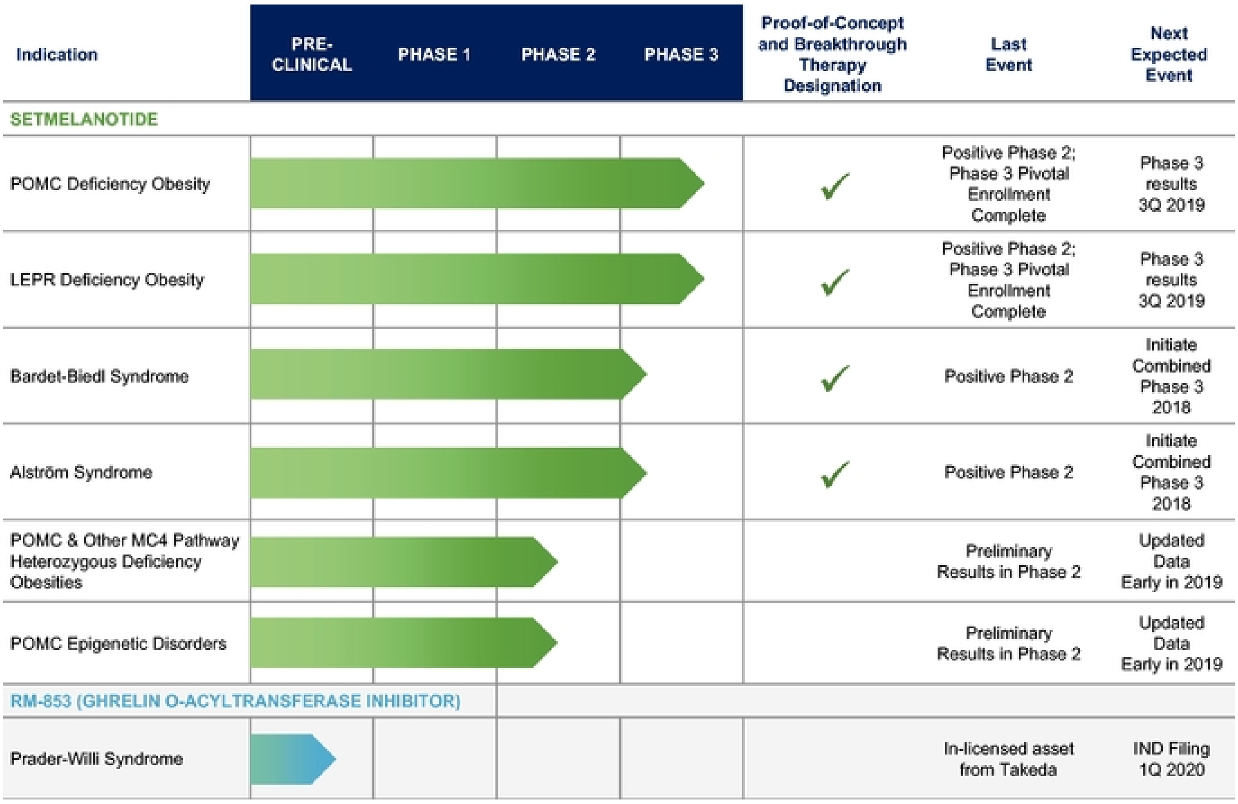
- **Expand setmelanotide development to additional upstream MC4 pathway deficiencies, including POMC heterozygous deficiency obesity and POMC epigenetic disorders.** We believe we can leverage our experience with and mechanistic understanding of the MC4 pathway to advance development of setmelanotide for other upstream MC4 pathway deficiencies. We have an ongoing Phase 2 clinical trial that includes patients with these rare genetic disorders, and reported initial, preliminary results in these indications in June 2018. We continue to investigate other potential indications that may result from MC4 pathway deficiencies, in which we may study treatment with setmelanotide in the future.

- **Commercialize setmelanotide for rare disease indications in core strategic markets.** We intend to establish our own commercial sales and marketing organization in the United States and other core strategic markets. We expect this sales organization will target physicians treating these rare genetic disorders of obesity, including pediatric and adult endocrinologists. We believe that building our own commercial operations will deliver a greater return on our product investment than if we license the rights to commercialize these products to third parties. We may also selectively establish partnerships in markets outside the United States for sales, marketing, and distribution.

- **Leverage the broad experience of our team in clinical and commercial drug development, and product acquisitions.** We will apply our team's extensive experience in developing and commercializing innovative medicines to the development and launch of setmelanotide. We will apply similar expertise to advance our second product candidate, RM-853, from pre-clinical to clinical development. In addition, we intend to identify and acquire new pipeline product candidates in related diseases. Our team is complemented by highly experienced external consultants and collaborators in the areas of drug discovery, development, manufacturing and regulatory approval.

Our Product Pipeline

The following chart depicts key information regarding the development of setmelanotide, including the indications we are pursuing within MC4 pathway deficiencies, the current state of development and our expected upcoming milestones:



Market Overview

Recent Advances in the Understanding of Obesity

Diet and lifestyle modifications remain the cornerstones of weight loss therapy, but they are limited by a lack of long-term success for most obese patients. The long-term efficacy of these interventions and for existing drug therapies is often limited by the counter-regulatory mechanisms of the human body. For example, with diet induced weight loss, typically there is a large decrease in energy expenditure that offsets that weight loss. Accordingly, the discovery that the MC4 pathway can regulate both appetite and energy homeostasis separately—helping maintain the balance between food intake and energy burn—has defined an important target for therapeutics. In addition to POMC deficiency obesity and LepR deficiency obesity, recent advances in genetic studies have identified several diseases that are the result of genetic defects affecting the MC4 pathway, including Bardet-Biedl syndrome, Alström syndrome, POMC heterozygous deficiency obesity, and POMC epigenetic disorders. With a deeper understanding of this critical signaling pathway, we are taking a different approach to drug development by focusing on specific genetic deficiencies affecting the MC4 pathway. We believe that this approach has the potential to provide dramatic improvements in weight and appetite by restoring lost function in the MC4 pathway.

Obesity Caused by Rare Genetic Deficiencies Affecting the MC4 Pathway

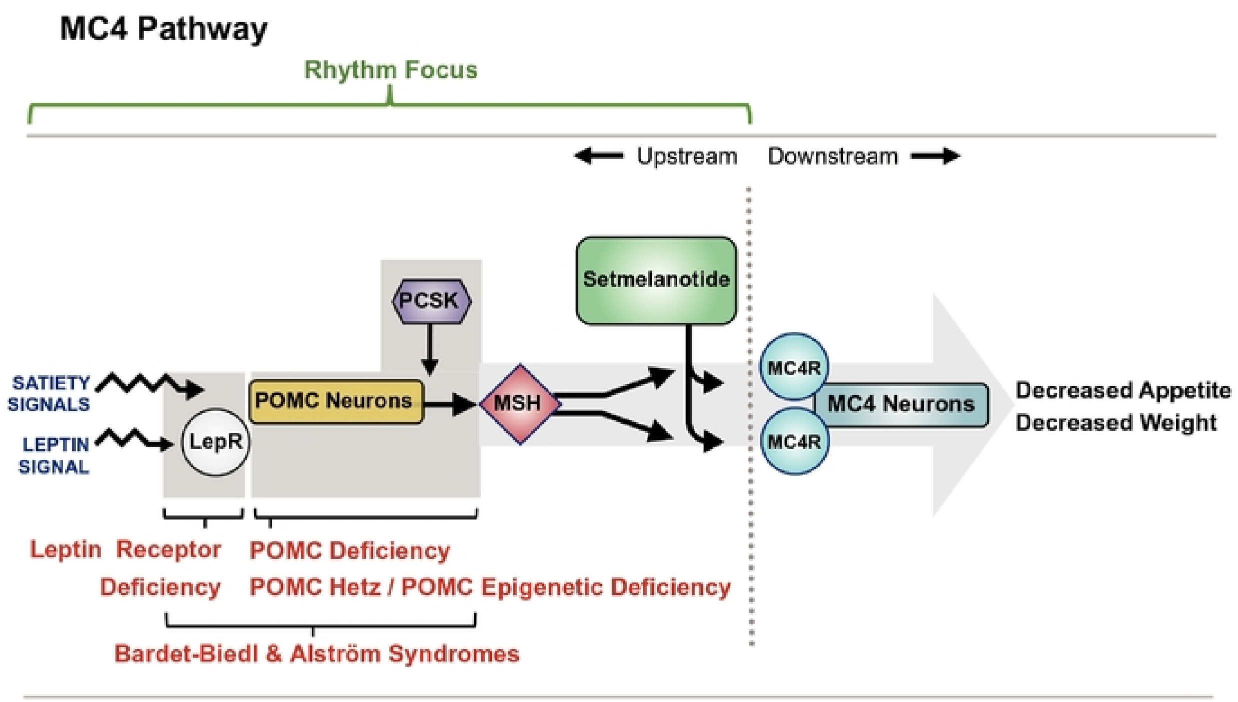
The MC4 pathway serves a critical role in the control of food intake and energy balance. Its activity decreases appetite and caloric intake, and increases energy expenditure, with MC4R acting as the final step in the signaling pathway. This important hypothalamic, or lower brainstem, pathway has been the focus of extensive investigation for many years, and we have a deep understanding of this mechanism, which is unlike the targets of most other anti-obesity therapies. As a result, we believe we can better predict the efficacy and safety profile expected from modulating this target. The critical role of the MC4 pathway in weight regulation was also validated with the discovery that single genetic defects at many points in this pathway result in early onset, severe obesity.

The MC4 pathway is illustrated in the figure below, from the activation of the pathway to the resulting decrease in appetite and weight. Under normal conditions, POMC neurons are activated by brain satiety signals, including those resulting from the hormone leptin acting through LepR. POMC neurons produce a protein, which is specifically processed by the proprotein convertase subtilisin/kexin 1, or PCSK, enzyme, into melanocyte stimulating hormone, or MSH, the natural ligand, or activator, for MC4R. When genetic mutations disrupt this pathway, the result is hyperphagia and severe obesity.

We are focused on developing setmelanotide for genetic disorders that result in defects in this pathway that are upstream of MC4R. Setmelanotide has the potential to restore lost function in this pathway by activating the intact MC4 pathway below the genetic defect. In this way, we believe setmelanotide acts as replacement therapy.

The figure below also illustrates some of the upstream MC4 pathway deficiencies that are the targets of our development activities.

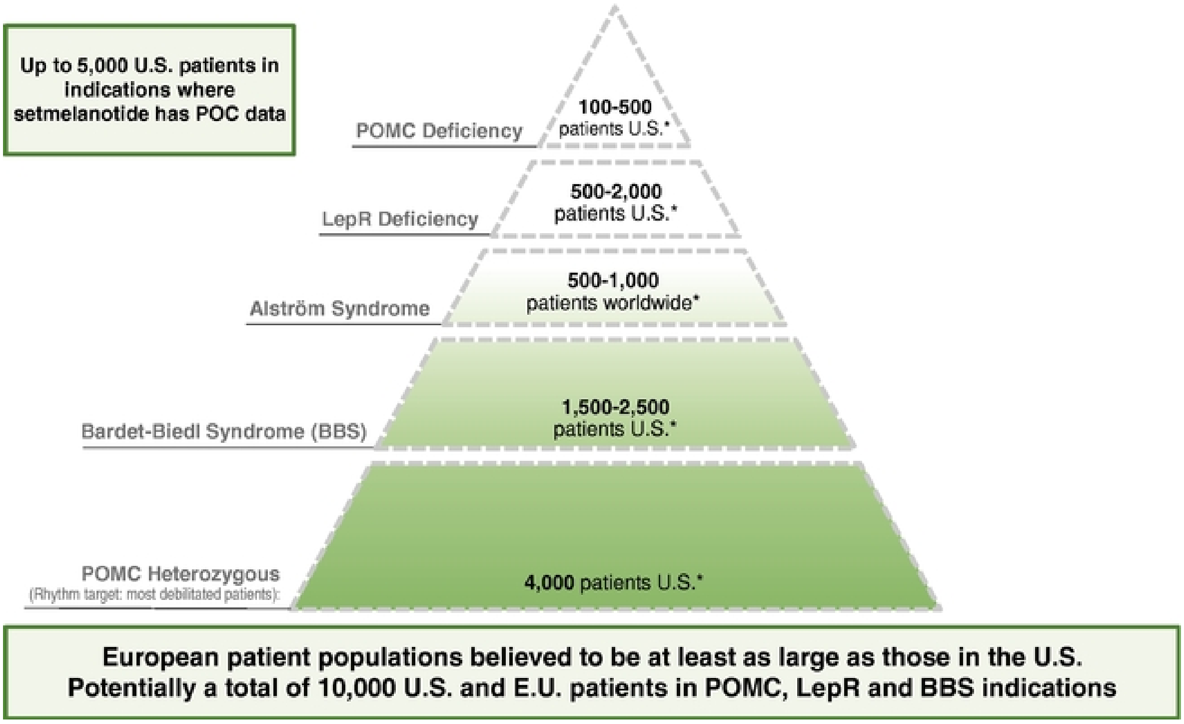
Setmelanotide Development Targets: Upstream Deficiencies Affecting the MC4 Pathway



Epidemiology of Rare Genetic Disorders of the MC4 Pathway

Clinical Epidemiology

The figure below summarizes the indications on which we are focusing for the development of setmelanotide, including our clinical epidemiology estimates for the addressable patient populations within these indications.



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* The patient numbers above are based on Company estimates from clinical publications.
† Epidemiological estimates are not yet available for POMC epigenetic disorders.

We believe that the patient populations in the European Union are at least as large as those in the United States. However, we do not have comparable epidemiological data from the European Union and these estimates are therefore based solely on applying relative population percentages to the Company-derived estimates described above.

Genetic Epidemiology Studies

We have estimated the patient populations for our rare genetic disorders of obesity primarily by identifying patients or by estimating from clinical epidemiology information. Another method to estimate the size of these ultra-rare populations is by genetic epidemiology using newly available large genomic databases of either full genome or exome sequences. We have begun some substantial efforts, both directly and with collaborators, with a series of such databases. Much of our preliminary work has utilized a database of approximately 140,000 genomes, representative of the U.S. population. The results of this analysis were published in May 2018 in the Journal of Clinical Endocrinology and Metabolism, a leading journal in this field, which we believe validates the scientific and epidemiological importance of our findings.

The results from this effort have been supportive of our clinical epidemiological estimates, even when using conservative genetic epidemiology assumptions. The results support estimates of the number of patients in the United States who are homozygous deficient in the POMC gene, which is one of the two genetic defects causing POMC deficiency obesity, and who are homozygous deficient in the LepR gene, are at least as large, or larger than, our clinical epidemiology assumptions, as provided above. In addition, the estimates of patients who are homozygous deficient in the PCSK1 gene, which is the other genetic defect causing POMC deficiency obesity, may be substantially larger than our clinical epidemiology assumptions. Overall, our clinical epidemiology based estimates for POMC deficiency obesity (up to 500 U.S. patients including both POMC and PCSK1 gene disorders) and LepR deficiency obesity (up to 2,000 U.S. patients) support up to 2,500 U.S. patients combined. Our preliminary genetic epidemiology estimates suggest a total of approximately 13,000 U.S. patients with these disorders, representing a 5-fold increase in our clinical epidemiology based estimates.

We have already begun to expand our genetic epidemiology analysis into other genomic databases that contain patients with different demographics, and are actively working with a series of academic and industry collaborators. Our published data support that while individual mutations may cluster in specific demographic groups, these rare genetic disorders are seen widely across the demographic spectrum. The ongoing expansion of genomic data available in other forums also has the effect of supporting this effort. An important improvement in this effort will be working with data linked to phenotypic information to better characterize the genetic information we are analyzing.

We believe the separate analyses that we have completed using clinical epidemiology and genetic epidemiology provide a robust range of patient population estimates for these rare disorders. However, to be conservative, we reference the clinical epidemiology figures in our descriptions of our target indications.

Obesity Caused by Upstream Genetic Deficiencies Affecting the MC4 Pathway

We have completed four positive Phase 2 trials of setmelanotide that provide proof of concept for four upstream MC4 pathway genetic defects in which obesity is life-threatening but the downstream MC4 pathway is fully functional. For POMC deficiency obesity, LepR deficiency obesity, and Bardet-Biedl syndrome, we estimate an aggregate addressable population of up to 5,000 people in the United States. In addition, we estimate that Alström syndrome has an addressable patient population of up to 1,000 people worldwide.

POMC Deficiency Obesity

POMC deficiency obesity is an ultra-rare genetic disorder, with severe, early onset obesity, defined here as a body mass index, or BMI, of greater than 40 kg/m^2, and hyperphagia as hallmark clinical features. Patients with POMC deficiency obesity are extremely rare. There are approximately 50 patients with POMC deficiency obesity noted in a series of published case reports, each mostly reporting a single or small number of patients. However, we estimate that our addressable patient population for this disorder is approximately 100 to 500 patients in the United States, as most of the reported cases are from a small number of academic research centers, and because genetic testing for POMC deficiency is often unavailable and rarely performed. However, our genetic epidemiological estimates are several times higher. Most patients are not currently diagnosed and based on discussions with experts in rare diseases, we believe the number of diagnosed cases will markedly increase with increased awareness of this disorder and the availability of new treatments.

POMC deficiency obesity is caused by the loss of both genetic copies of either the gene for POMC or the gene for PCSK. This results either in loss of POMC neuropeptide synthesis, in the case of homozygous deficiency in the POMC gene, or in disruption of the required processing of the POMC neuropeptide product to MSH by the PCSK enzyme, in the case of homozygous deficiency in the PCSK gene. The end result of both of these two homozygous genetic defects is lack of MSH to bind and activate MC4R, ultimately leading to the lack of stimulation of downstream MC4 neurons and causing severe, early onset obesity and hyperphagia. POMC homozygous deficiency may also be associated with hormonal deficiencies, such as hypoadrenalism, as well as red hair and fair skin.

POMC deficiency is characterized by voracious infant feeding, rapid weight gain and severe obesity, often in early infancy, with patients demonstrating remarkable weight increases many standard deviations from the normal weight growth curves. These patients and their caregivers have attempted to stabilize body weight with the help of psychologists, nutritionists and pediatric endocrinologists, all without significant success. We have completed enrollment in the pivotal cohorts for our POMC deficiency obesity Phase 3 clinical trial, and expect to report initial Phase 3 data in the third quarter of 2019. Currently there are no approved or effective therapies for POMC deficiency obesity.

Leptin Receptor Deficiency Obesity

LepR deficiency obesity is an ultra-rare genetic disorder that causes hyperphagia and severe, early onset obesity. LepR deficiency accounts for an estimated 1% of cases of severe, early onset obesity. Based on clinical epidemiology studies in small cohorts of patients with severe, early onset obesity, we estimate that our addressable patient population for this disorder is approximately 500 to 2,000 patients in the United States, though our genetic epidemiological estimates suggest the number may be moderately higher.

Leptin's role in obesity has been elucidated by characterization of severely obese people with homozygous mutations that impair the activity of leptin, including disruption of signaling at the LepR, known as LepR deficiency obesity. Under normal conditions, leptin can activate POMC neurons and the downstream MC4, but like other deficiencies upstream in the MC4 pathway, lack of signaling at LepR results in loss of function in the MC4 pathway.

Like POMC deficiency obesity, patients with LepR deficiency obesity exhibit hyperphagia and severe obesity from early childhood. LepR deficiency is also associated with hypogonadism and reduced immune function. We have completed enrollment of the pivotal cohort for our LepR deficiency obesity Phase 3 clinical trial, and expect to report initial Phase 3 data in the third quarter of 2019. It is our intention, pending discussions with the FDA, to file our NDA for LepR deficiency obesity concurrently with our NDA for POMC deficiency obesity, as enrollment of our pivotal cohort completed almost simultaneously. Currently there are no approved or effective therapies for LepR deficiency obesity.

Bardet-Biedl Syndrome

Bardet-Biedl syndrome is a life-threatening, ultra-rare orphan disease with a prevalence of approximately one in 100,000 in North America. We estimate that our addressable patient population for Bardet-Biedl syndrome obesity is approximately 1,500 to 2,500 patients in the United States. Bardet-Biedl syndrome is a monogenic disorder that causes severe obesity and hyperphagia as well as vision loss, polydactyly, kidney abnormalities, and other signs and symptoms. For Bardet-Biedl syndrome patients, hyperphagia and obesity can have significant health consequences.

Bardet-Biedl syndrome is part of a class of disorders called ciliopathies, or disorders associated with the impairment of cilia function in cells. Cilia are hair-like cellular projections that play a fundamental role in the regulation of several biological processes, including satiety signaling. Cilia dysfunction is thought to contribute to hyperphagia and obesity in Bardet-Biedl syndrome. Bardet-Biedl syndrome is a genetically heterogeneous disease that is caused by as many as 21 separate Bardet-Biedl loci defects that result in a similar syndrome, though each Bardet-Biedl syndrome patient only has one of these defects.

Recent scientific studies identify deficiencies affecting the MC4 pathway as a potential cause of the obesity and hyperphagia associated with Bardet-Biedl syndrome and demonstrate that an MC4R agonist can directly impact these symptoms. Studies in mouse models of Bardet-Biedl syndrome show that deficiencies in the MC4 pathway contribute to the obesity and hyperphagia in Bardet-Biedl syndrome, with animals developing hyperphagic tendencies as early as 10 weeks of age. Notably, these mice have decreased leptin receptor signaling, with the essential hallmarks of failure to activate POMC neurons. The potential utility of MC4 agonists is also supported by studies in Bardet-Biedl syndrome rodent models, where mice have responded to an MC4 agonist resulting in reduced food intake and body weight. We have demonstrated proof of concept in Bardet-Biedl syndrome indicating that this is also a setmelanotide-responsive, upstream MC4 pathway disorder. We reported preliminary Phase 2 results for Bardet-Biedl syndrome in the fourth quarter of 2017 and updated the clinical status of these patients in the second quarter of 2018. We have had discussions with the FDA on Phase 3 design and we are in the process of submitting a draft Phase 3 protocol for FDA review. The FDA has preliminarily indicated that this Phase 3 trial will include both Bardet-Biedl syndrome and Alström syndrome patients. We expect to enroll patients in this Phase 3 trial before the end of 2018. Currently there are no approved or effective therapies for Bardet-Biedl syndrome.

Alström Syndrome

Alström syndrome is a life-threatening, ultra-rare orphan disease with a prevalence of approximately one in 1,000,000 in North America. We estimate that our addressable patient population for Alström syndrome is approximately 500 to 1,000 patients worldwide. Alström syndrome is a monogenic disorder that causes childhood obesity and hyperphagia as well as progressive vision loss, deafness, cardiomegaly, insulin resistance and other signs and symptoms. Variable features include short stature, cardiomyopathy, and progressive lung, liver, and kidney dysfunction. Symptoms of Alström syndrome first appear in infancy, and progressive development of multi-organ pathology leads to a reduced life expectancy, with survival rare beyond the age of 50.

Alström syndrome is a ciliopathy caused by mutations in the ALMS1 gene, which has been shown to be important for cilia function. Like Bardet-Biedl syndrome, recent scientific studies identify genetic deficiencies affecting the MC4 signaling pathway as a potential cause of the obesity and hyperphagia associated with Alström syndrome. Studies in a mouse model of Alström syndrome show a reduction in the number of cilia in specific neurons in the hypothalamus that are critical for MC4 pathway signaling. While Alström syndrome is less well studied than Bardet-Biedl syndrome, the similar pathophysiology of cilial dysfunction and clinical presentation support that deficiencies in the MC4 pathway are implicated in the obesity and hyperphagia observed in Alström syndrome. We believe we have demonstrated proof of concept in our Phase 2 clinical trial in Alström syndrome and met with the FDA in May 2018 to discuss a combined pivotal Phase 3 clinical trial in both Bardet-Biedl syndrome and Alström syndrome. Based on these preliminary discussions with the FDA, we currently plan to initiate this trial and enroll patients in 2018. Currently there are no approved or effective therapies for Alström syndrome.

Other Upstream Genetic Defects in the MC4 Pathway

In addition to POMC deficiency obesity, LepR deficiency obesity, Bardet-Biedl syndrome, and Alström syndrome, there are other upstream, MC4 pathway deficiencies for which we believe setmelanotide may function as replacement therapy, including defects that partially modulate POMC activity, such as POMC heterozygous deficiency obesity and POMC epigenetic disorders.

POMC Heterozygous Deficiency Obesity

POMC heterozygous deficiency results in a strong predisposition to obesity, though the epidemiology and clinical characterization of these patients is less well known. POMC heterozygous deficiency obesity is caused by the loss of one of the two genetic copies of either the gene for POMC or the gene for PCSK. An estimated 2% of severe, early onset obesity patients have POMC heterozygous deficiency obesity, which is much more common than the ultra-rare POMC deficiency obesity in which both copies of either the POMC or PCSK genes are impaired. We believe that the most severe POMC heterozygous deficiency obesity patients may be suitable for treatment with setmelanotide. We estimate that our addressable patient population within severe POMC heterozygous deficiency obesity is approximately 4,000 patients in the United States, based on epidemiology studies in small cohorts of patients with severe early onset obesity and adult obesity. Animal models support that such heterozygous deficiency in the critical

MC4 pathway can result in a strong predisposition to severe obesity. The effect of heterozygous deficiency was first demonstrated in MC4R heterozygous deficiency obesity.

We are also studying patients with other MC4 pathway gene heterozygous mutations, including patients with heterozygous mutations in genes such as LepR and Bardet-Biedl, as well as patients with heterozygous mutations in more than one gene in the MC4 pathway. For simplicity, in this prospectus we refer to the group of such heterozygous patients as patients with POMC heterozygous deficiency, but we will be transitioning to more general language, such as patients with Heterozygous Mutations in the MC4 Pathway, as more of these patients enter our Phase 2 trials.

It is thought that the obesity of patients with POMC heterozygous deficiency may have a broader spectrum of severity than POMC deficiency obesity. Therefore, our focus will be on the most severe of the POMC heterozygous deficiency obesity patients, with our estimate that only a small percentage of these patients will benefit from targeted therapy with substantial efficacy. As a result, we have initiated a Phase 2 proof of concept trial to confirm our hypothesis that the subset of patients with very severe POMC heterozygous deficiency obesity may be highly responsive to setmelanotide therapy. We have an ongoing Phase 2 clinical trial in POMC heterozygous deficiency obesity and reported initial, preliminary results in June 2018. There are currently no approved or effective therapies for POMC heterozygous deficiency obesity.

POMC Epigenetic Disorders

Recent scientific studies have identified patients with obesity due to a partial lack of MSH that is caused by epigenetic POMC variant. Given the recent discovery of these epigenetic disorders, there is currently no epidemiology data that defines the prevalence of POMC epigenetic disorders. However, we believe that these are rare disorders. Epigenetics implies DNA modifications, which can change gene expression without altering the DNA sequence itself. The most stable epigenetic modification is called DNA methylation. Recently, our academic collaborators in Berlin have described a POMC hypermethylation variant, which correlates with increased body weight in children and adults. Therefore, the presence of the POMC epigenetic variant leads to an increased risk of obesity based on reduced POMC gene activity. We expect that these patients under-express the POMC gene product and as a result have a partial MSH deficiency. We have initiated a Phase 2 proof of concept trial to confirm our hypothesis that the subset of patients with very severe POMC epigenetic disorders may be highly responsive to setmelanotide therapy. We have an ongoing Phase 2 clinical trial in POMC epigenetic disorders and reported initial, preliminary results in June 2018. We plan to provide a further update for these indications early in 2019. There are currently no approved or effective therapies for these disorders.

Obesity Caused by Downstream Genetic Deficiencies Affecting the MC4 Pathway

MC4 Receptor Heterozygous Deficiency Obesity

MC4 Receptor, or MC4R, heterozygous deficiency is caused by the absence or loss of function of one genetic copy of the gene for MC4R. Consistent with POMC heterozygous deficiency, MC4R heterozygous deficiency results in a strong predisposition to early onset and severe obesity. MC4R heterozygous deficiency is the most common genetic cause of obesity. An epidemiological study performed in Europe in 2006 reported a prevalence of 2.6% of genetic defects in the MC4R gene in the obese population with a BMI of greater than 30 kg/m^2, and studies performed in both Europe and the United States in 2000 and 2003, respectively, reported a prevalence of up to 4% of these genetic defects in more severely obese populations with a BMI of greater than 35 kg/m^2. These prevalence rates suggest that there are approximately one million people in the United States with obesity caused by a mutation of the MC4R gene.

These patients have a higher risk than the general population for early onset obesity and complications such as diabetes. Furthermore, MC4R deficiency may offset the beneficial effects of diet and exercise for sustained weight loss, limiting treatment options for these individuals. There are currently no approved or effective therapies for MC4R heterozygous deficiency obesity.

While setmelanotide appears to show strong efficacy in a Phase 1b trial for the treatment of MC4R heterozygous deficiency obesity patients, it is downstream of where setmelanotide interacts with the MC4R, and we are currently focusing instead on genetic defects that are upstream of the MC4R. This is because we believe that many of these upstream genetic disorders cause even more severe, often life-threatening obesity, and because setmelanotide has the potential to restore lost function in these upstream disorders, delivering more compelling efficacy. We have conducted additional research that was published in Nature Medicine in May 2018, which suggests that a sizable number of individuals with obesity who carry MC4R mutations, and were previously assessed functionally normal, may respond to setmelanotide treatment. This may open the possibility of new indications for setmelanotide in the future.

Expanding Attention to the Diagnosis of Genetic Obesity

The Endocrine Society issued new Pediatric Obesity Guidelines in January 2017 that, for the first time, recommend genotyping patients with severe pediatric obesity and hyperphagia. These guidelines estimate that up to 7% of patients with extreme pediatric obesity have a genetic mutation, including genetic MC4 pathway deficiencies, that drives their obesity. The guidelines also suggest that this percentage of severe pediatric obesity patients will increase, with newer methods and wider awareness of the need for genetic testing.

We are supporting several initiatives to expand the diagnosis of genetic obesity, including The Genetic Obesity Project. The Genetic Obesity Project has initiated a genotyping study, called GO-ID, and a patient registry, called TEMPO, both focusing initially on identifying people with POMC deficiency obesity and LepR deficiency obesity and which we intend to expand to include other MC4 pathway deficiencies. We will be expanding our panel of obesity-related genes used in our GO-ID study in the second half of 2018. The preliminary results, in 560 patients, from the GO-ID study suggest that patients with these disorders can be successfully identified.

We are also conducting genetic obesity epidemiology analysis of MC4 pathway genetic defects in a large representative sample of the U.S. population, and we expect to expand the genetic databases in our research efforts on an ongoing basis. The first results of this research were published in May 2018 in the Journal of Clinical Endocrinology and Metabolism, a leading journal in this field. An important improvement in this effort will be working with data linked to phenotypic information to better characterize the genetic information we are analyzing. In addition, we tested associations between BMI and loss of function mutation burden in various populations to further define the MC4 pathway and its potential impact on obesity, showing that the cumulative allele burden, or number of mutations along the MC4 pathway in a single individual, predisposes to more obesity.

Limitations of Current Therapies

Although drugs approved for general obesity can potentially be used in obese patients with MC4 pathway deficiencies, all have limited efficacy and aim to treat symptoms rather than addressing the underlying biology. There are currently no treatments approved specifically for obesity and hyperphagia in POMC deficiency obesity, LepR deficiency obesity, Bardet-Biedl syndrome, Alström syndrome, POMC heterozygous deficiency obesity, or POMC epigenetic disorders. Bariatric surgery is not an option in patients with upstream defects in the MC4 pathway who have severe obesity and hyperphagia.

Setmelanotide: A First-in-Class MC4R Agonist in Two Phase 3 Programs

Setmelanotide is a potent, first-in-class, MC4R agonist peptide administered by daily SC injection. Setmelanotide is in Phase 3 for the treatment of two rare genetic disorders of obesity caused by MC4 pathway deficiencies, and we are initiating a combined Phase 3 clinical trial in two additional rare genetic disorders. We also have an ongoing Phase 2 clinical trial in two other MC4 pathway disorders. MC4R modulates a key pathway in humans that regulates energy homeostasis and food intake.

The critical role of the MC4 pathway in weight regulation was validated with the discovery that single genetic defects in this pathway result in severe, early onset obesity. The first generation MC4R agonists were small molecules that failed in clinical trials primarily due to safety issues, particularly increases in blood pressure, as well as limited efficacy. In contrast, setmelanotide is a peptide that retains the specificity and functionality of the naturally occurring hormone that activates MC4R. In total, approximately 300 obese subjects and patients have been treated with setmelanotide in previous and ongoing clinical trials in which setmelanotide demonstrated significant weight loss with good tolerability.

Clinical Development in Rare Genetic Disorders of Obesity Caused by MC4 Pathway Deficiencies

Setmelanotide is currently in Phase 3 development for POMC deficiency obesity and LepR deficiency obesity, and we are initiating a combined Phase 3 trial for Bardet-Biedl syndrome and Alström syndrome. We have completed enrollment in the pivotal cohorts for both our POMC deficiency obesity Phase 3 clinical trial and our LepR deficiency obesity Phase 3 clinical trial. We expect to report initial Phase 3 data from these trials in the third quarter of 2019, and subsequently plan to file for regulatory approval for these two indications concurrently. We believe that we have demonstrated proof of concept in our Phase 2 clinical trial in Bardet-Biedl syndrome and in Alström syndrome, and met with the FDA in May 2018 to discuss a combined pivotal Phase 3 clinical trial in both Bardet-Biedl syndrome and Alström syndrome. Based on these preliminary discussions with the FDA, we currently plan to initiate this trial and enroll patients in 2018. We continue to study setmelanotide in these indications in Phase 2 development in long-term extensions. We are also enrolling patients for the treatment of other rare monogenic disorders of obesity, including POMC and other heterozygous deficiency obesity, and POMC epigenetic disorders. We hypothesize that all of these disorders are genetically defined deficiencies upstream in the MC4 pathway.

We are enrolling patients in two very similar Phase 2 clinical trials, each of which is designed to capture a broad range of indications under one investigational protocol, or a basket study. We believe that we have demonstrated proof of concept both in Bardet-Biedl syndrome and in Alström syndrome, indicating that these closely related syndromes are also setmelanotide-responsive, upstream MC4 pathway disorders. We reported initial, preliminary results for POMC heterozygous deficiency obesity and POMC epigenetic patients in June 2018. We plan to provide a further update for these indications early in 2019. We have also completed a Phase 2 trial in PWS.

Based on FDA consultations to date, and the FDA granting Breakthrough Therapy designation for POMC deficiency obesity and LepR deficiency obesity, and including Bardet-Biedl syndrome and Alström syndrome under the existing Breakthrough Therapy designation for setmelanotide, we believe we can seek indications for obesity caused by upstream defects in the MC4 pathway with rapid paths to approval, as compared to typical obesity drug candidates, because of the high unmet need and rare prevalence of these disorders. We expect to use the results of our Phase 3 clinical trials of setmelanotide in POMC deficiency obesity and LepR deficiency obesity, which will run concurrently, as the foundation for proceeding directly to approval for these indications.

We believe our data in POMC deficiency obesity, LepR deficiency obesity, Bardet-Biedl syndrome, and Alström syndrome provide strong proof of concept that setmelanotide, when targeted for deficiencies affecting the upstream portion of the MC4 pathway, can provide compelling efficacy for weight loss and decrease in hunger. Proof of concept for substantial weight loss in patients with downstream, heterozygous mutations of the MC4R gene itself has also been achieved in a small, four-week, Phase 1b clinical trial. While these downstream defects are not our current area of focus, based on new scientific research, we believe there is evidence supporting the potential for substantial weight loss efficacy in a setting of a partially defective, downstream defect in the MC4 pathway, which impacts a significantly larger population.

Initial setmelanotide clinical trials were in patients with general obesity, which provided preliminary evidence of the safety and efficacy of the drug, and were the foundation for the Phase 2 trials in rare genetic disorders of obesity. In these trials, setmelanotide has generally achieved weight loss without adversely increasing blood pressure. These trials in the general obese population are described below.

The following table outlines our ongoing and planned setmelanotide trials in rare monogenic disorders of obesity.

Setmelanotide: Key Clinical Programs in Monogenic MC4 Pathway Disorders of Defined Obesity

	POMC Deficiency Pivotal	LepR Deficiency Pivotal	POMC/LepR Deficiency Proof of Concept	Other Populations Proof of Concept Basket Protocols(6)
Clinical trial phase	Phase 3	Phase 3	Phase 2	Phase 2
Status	Enrollment completed 2Q2018	Enrollment completed 2Q2018	Initiated 2014, Completed 4Q 2016 for these indications(5)	Initiated 2016(7)(8)
Treatment groups(1)	Setmelanotide(2)	Setmelanotide(2)	Setmelanotide	Setmelanotide
Number of patients	10(3)	10(3)	2 POMC, 3 LepR	20-100(9)
Patient demographics	Adult/pediatric POMC deficient(4)	Adult/pediatric LepR deficient(4)	Adults/Adolescents	Adult/pediatric(4) Multiple indications: Bardet-Biedl syndrome; Alström syndrome; POMC heterozygous deficiency obesity; POMC epigenetic disorders, and others
Duration of treatment	52 weeks + Extensions	52 weeks + Extensions	12 weeks + Extensions	12 weeks + Extensions
Location	United States, Germany, Canada, United Kingdom, France, Belgium	United States, Germany, United Kingdom, France(10)	Germany	United States, Germany, United Kingdom, France

	Extension to ongoing Protocols	TEMPO Registry Study	BBS/Alström Syndrome Pivotal(16)	Natural History Study
Clinical trial phase	Extension	Prospective Registry cohort	Phase 3	Natural History observational cohort
Status	Initiating 2H2018	Initiating 2H2018	Initiating, first patients to be enrolled in 2018	Initiated 4Q2017
Treatment groups(1)	Setmelanotide(11)	No treatment(14)	Setmelanotide(17)	No treatment(14)
Number of patients	Up to 100 patients(12)	Up to 1000 patients	At least 20 BBS At least 6 Alström's	10-20
Patient demographics	Any patient completing another setmelanotide clinical protocol(13)	Various(15)	Adult/Pediatric	Adult/pediatric(19) Patients with POMC or LepR deficiency obesity
Duration of treatment	Multi-year Extensions	Open ended	52 weeks + Extensions(18)	Up to 5 years
Location	Initiating in multiple countries	Initiating in multiple countries	To be determined	To be determined

(1) Setmelanotide, administered as once daily SC injection, except for TEMPO Registry study and Natural History study.
(2) These trials include a placebo controlled, double-blind withdrawal period.
(3) Approximately 10 POMC deficiency obesity and 10 LepR deficiency obesity patients will be included in the pivotal cohort for each trial, but in agreement with the FDA, additional patients can be recruited who will not have reached one year of treatment at the time of NDA.
(4) POMC deficiency includes homozygous deficiency in either the POMC or PCSK genes; pediatric patients ³ six years are currently being studied, though it is likely that the lower age pediatric patients will have less than one year of treatment at the time of NDA filing. We expect to enroll pediatric patients in our LepR deficiency obesity pivotal trial starting in 2018, and similarly for basket protocols.
(5) This trial will continue as a basket protocol and study additional indications.
(6) Basket protocols study a variety of different indications or patient populations administratively in one protocol, though each population is enrolled and analyzed separately.
(7) One of our proof of concept basket protocols was originally the Phase 2 trial for POMC deficiency obesity and LepR deficiency obesity initiated in Germany in 2016 and provided proof of concept in these indications. This trial was later amended in 2016 to

include other MC4 pathway disorders. Our second basket protocol is open, or is being opened in other geographical locations (United States 2016; United Kingdom, France in 2017).

(8) We have enrolled patients with Bardet-Biedl syndrome, Alström syndrome, and POMC epigenetic disorders, as well as patients with POMC and other MC4 pathway gene heterozygous mutations, and anticipate additional indications for study possibly later in 2018 or early 2019.
(9) We are studying, or plan to study less than 10 patients with Bardet-Biedl syndrome, less than five with Alström syndrome, but are studying, or plan to study a larger number of patients with other MC4 pathway indications, such as heterozygous and epigenetic patients, indications with potentially more complexity.
(10) We have ongoing trials approved in the United States, Germany, United Kingdom, France and the Netherlands, and other countries may be included.
(11) All patients will receive open label setmelanotide in the extension protocol.
(12) It is anticipated that all patients in any setmelanotide treatment protocol will be transferred over to the extension protocol for long-term follow-up after completing a minimum one year of treatment in another setmelanotide treatment protocol.
(13) Only patients who have been in another setmelanotide treatment protocol can enter an extension.
(14) Patients in the TEMPO registry and Natural History study will not receive treatment.
(15) Individual subjects enrolled in this registry will need to meet both (1) phenotypic, or BMI, and (2) genotypic entry criteria that fit a working definition of extreme obesity associated with confirmed or putative MC4R pathway genetic variants.
(16) All protocol details for the Bardet-Biedl syndrome/Alström syndrome pivotal trial are preliminary, pending final discussions with the FDA.
(17) This trial may include a short randomized, placebo-controlled period for study validation, which is not anticipated to be a primary endpoint.
(18) Primary endpoint will be one year of treatment, anticipated to be similar to the endpoint for POMC deficiency obesity and LepR deficiency obesity pivotal trials.
(19) Patients two years or older may be enrolled.

Setmelanotide: Clinical Development Program in Genetically Defined Obesity

Phase 2 Clinical Development in POMC Deficiency Obesity

We have completed a Phase 2 proof of concept, open label clinical trial, Study RM-493-011, in two patients with POMC deficiency obesity in which these patients have been treated with setmelanotide for more than 2 years, resulting in profound reductions of hyperphagia and body weight, with good tolerability. The patients in this trial have provided proof of concept for the compelling effect of setmelanotide in this disorder. We are close to completing enrollment in the pivotal cohort of patients in our Phase 3 trial for this indication. The results of the Phase 2 trial were published in July 2016 in the New England Journal of Medicine, which we believe validates the scientific and clinical importance of our Phase 2 findings, and the accompanying editorial described the trial as demonstrating impressive hunger reduction and weight loss as well as improved insulin sensitivity. A brief update on these patients was also included in a publication in Nature Medicine in May 2018.

The first setmelanotide-treated patient was a 20-year-old woman, who at three months of age experienced the onset of obesity and hyperphagia. In spite of enormous efforts, the patient was never able to stabilize her body weight, except for brief periods, and she has remained hyperphagic. Ahead of our trial, the patient's self-reported trial hunger score was eight to nine out of 10 points, representing extreme hunger. She was entered into the trial at adulthood because of her severe obesity, with a baseline weight of 155 kg, or 341.7 lbs., and a BMI of 49.8 kg/m^2, and significant risk of comorbidities and a reduced life expectancy.

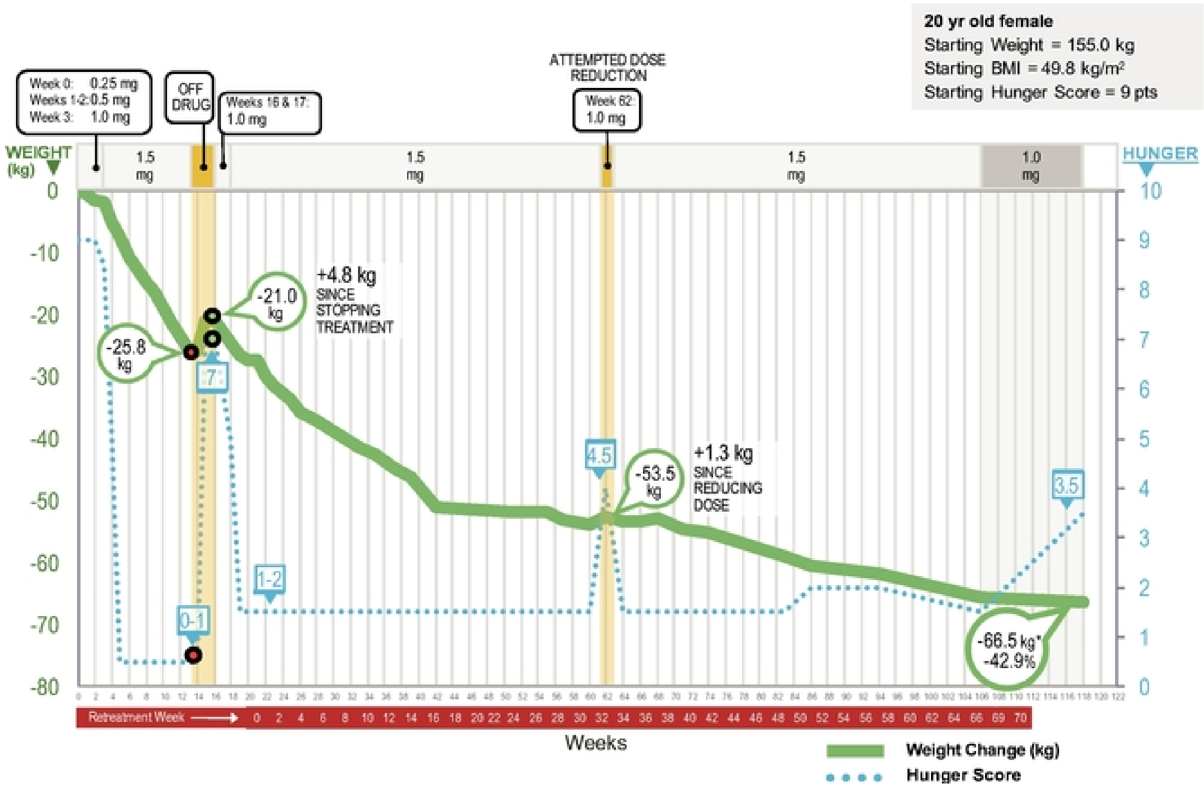
The trial, initially a 13-week, open label, ascending dose Phase 2 trial, was approved by the German Federal Institute for Drugs and Medical Devices, with open-label one-year extensions, and was planned to include approximately four to six patients with genetically confirmed POMC deficiency obesity. After efficacy-gated dose escalation, aiming for weekly weight loss of approximately two kg, or 4.4 lbs., the primary endpoint was weight loss, with other key endpoints including hunger score, body composition, insulin and glucose parameters, metabolic and cardiovascular risk factors, energy expenditure and general safety and tolerability.

After 13 weeks of therapy, with approximately the first four weeks at sub-therapeutic doses, our initial patient demonstrated weight loss of 25.8 kg, or 56.9 lbs., representing 16.7% of her initial body weight, with approximately two to three kilograms per week of weight loss demonstrated at the highest 1.5 mg/day dose.

Hunger scores, measured using a Likert score of zero to 10, where zero represents no hunger and 10 represents extreme hunger, mirrored the rate of weight loss, moving from scores of eight to nine prior to our trial to zero to one, as the patient was treated with increasing doses of setmelanotide. After termination of the 13-week main trial, the patient underwent a three-week withdrawal period off drug and regained 4.8 kg, or 10.6 lbs., with a return to moderate to severe hunger. Following approval to restart setmelanotide treatment, there was an immediate reduction of hunger and subsequently a continuation of body weight loss. This patient was on continuous treatment for 106 weeks, with a total weight loss of 65.6 kg, or 144.6 lbs., representing 42.3% of her initial body weight. There was no apparent difference in the rate of weight loss during the initial extension phase versus the main trial, however over time, the rate of weight loss has slowed, though this patient has continued to lose weight. The patient's need for continued therapy was supported by a short period of withdrawal after the patient had been treated for over one year. Reducing her daily dose from 1.5 mg/day to 1.0 mg/day resulted in an increase in her hunger scores from one to two points to four to five points, resulting in the patient requesting to be returned to her 1.5 mg/day dose, after which her hunger scores returned to one to two points. This data supports the physiological prediction that pharmacological treatment for this condition to suppress hunger will be required chronically. After approximately 106 weeks of treatment, her dose was reduced to 1 mg/day, and while her weight remained stable from week 106 to approximately week 130, her hunger scores increased to three to four points on the lower dose before returning to two points.

The results for this patient are shown in the figure below.

The Clinical Course of the Initial Patient in the Setmelanotide POMC Deficiency Obesity Phase 2 Trial through Week 118(1)



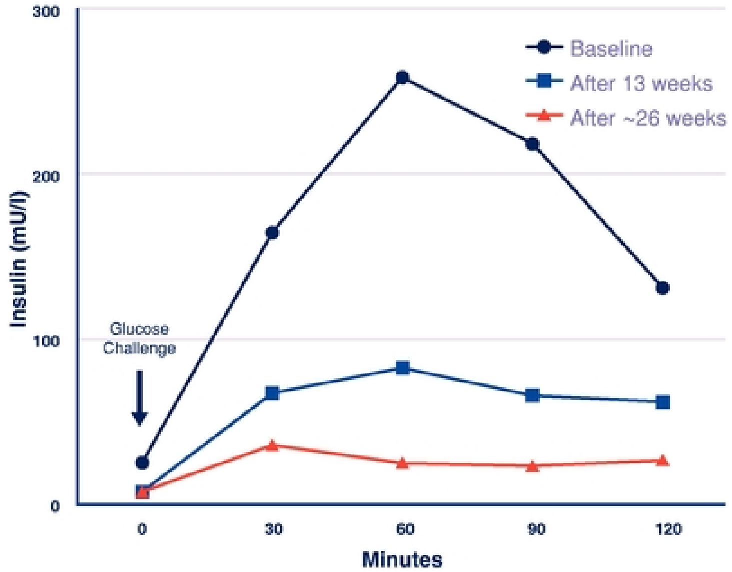
* Figures represent cumulative weight lost in kgs through approximately 118 weeks of treatment. See text for additional details.

(1) Daily setmelanotide dose adjustments over time are indicated at the top of the panel.

In general, diet induced weight loss in patients with general obesity is accompanied by significant counter-regulatory effects, including reductions in energy expenditure and increases in hunger. These lead to weight regain in the majority of patients. In contrast, the initial patient in our trial did not manifest these counter-regulatory responses, even after six months of therapy and a tremendous reduction of body weight. This data supports an effect of setmelanotide on energy expenditure independent from the profound effects on hyperphagia, corroborating results from previous trials of setmelanotide in patients with general obesity. Also of note, the reduction in body weight was mainly due to a loss of body fat mass, and lean body mass was not greatly altered. In this initial patient, setmelanotide was also associated with excellent tolerability, additional favorable changes in cardiovascular risk parameters, or lipids, and improvements in blood pressure and heart rate.

MC4R activation also causes improvements in glucose and insulin parameters in animal models, independent of weight loss. As shown in the figure below, for the initial patient in our POMC deficiency proof of concept trial, setmelanotide demonstrated a marked improvement in insulin resistance during treatment. While weight loss likely played an important role in this improvement, we believe the independent effect of MC4R agonism may also have contributed.

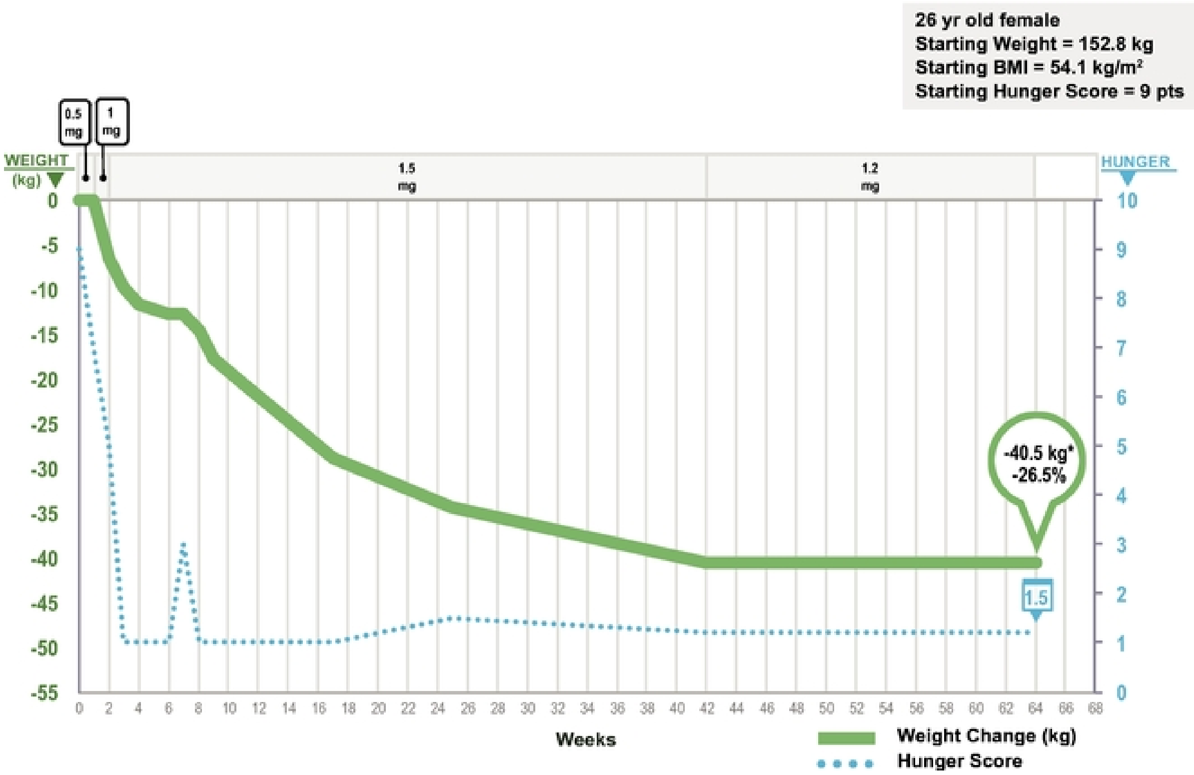
Setmelanotide Treatment Effects on Insulin Resistance (Insulin Response in Oral Glucose Tolerance Test) at Baseline, After 13 Weeks of Treatment (Phase 1), and at Approximately 26 Weeks During the Long-term Extension for our POMC Initial Patient



Results are also available for treatment with setmelanotide of a second patient with POMC deficiency obesity. The second patient is a 26-year-old woman who also experienced early onset of obesity and hyperphagia. Like the first patient, in spite of significant efforts, she was never able to stabilize her body weight, and she has remained hyperphagic. Ahead of our trial, the patient's self-reported trial hunger score was nine out of 10 points, representing extreme hunger, and her weight and BMI at trial entry were 152.8 kg, or 336.9 lbs., and 54.1 kg/m^2, respectively.

After 42 weeks of therapy at the 1.5 mg/day dose, our second patient demonstrated weight loss of 40.6 kg, or 89.5 lbs., representing 26.6% of her initial body weight, with approximately two to three kilograms per week of weight loss demonstrated initially. Hunger scores, measured using a Likert score of zero to 10, where zero represents no hunger and 10 represents extreme hunger, mirrored the rate of weight loss, with scores moving from nine prior to the trial to one on most weeks during the trial, as the patient was treated with increasing doses of setmelanotide. Similar to the initial patient, setmelanotide demonstrated an improvement in insulin resistance during treatment in our second POMC deficiency obesity patient. This patient continued on active treatment for 64 weeks on therapy and her weight stabilized at a weight loss of 40.5 kg, or 89.3 lbs. However, a non-serious febrile infection made an increase of the hydrocortisone treatment necessary. Due to a misunderstanding, this planned temporary elevated dosage of hydrocortisone was not returned to her basal dose of hydrocortisone after a few days as planned; as a result, her hunger feelings started to increase, with an associated increase in hunger score to 7 points, followed by weight gain. After adaptation of the hydrocortisone dosage during her next visit, the hunger feeling and weight decreased again and she has continued on treatment for 100 weeks in total.

The Clinical Course of our Second Patient in the Setmelanotide POMC Deficiency Obesity Phase 2 Trial through Week 64(1)



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* Figures represent cumulative weight lost in kgs through approximately 64 weeks of treatment. See text for additional details.
(1) Daily setmelanotide dose adjustments over time are indicated at the top of the panel.

Setmelanotide was generally well tolerated in the POMC deficiency obesity Phase 2 trial, with few adverse events, all mild and infrequent, and all previously reported in other clinical trials. These included reduced appetite and tanning of skin and nevi, or moles, intermittent and mild injection site reactions, and in rare instances tiredness, dry mouth, and gastrointestinal symptoms. The single serious adverse event was an influenza immunization reaction, which resulted in an overnight hospitalization and was considered unrelated to trial drug. A similar immunization reaction had occurred in this patient in a previous influenza immunization prior to treatment, and the patient has continued on setmelanotide since that event.

The results from the initial patients in our POMC deficiency obesity proof of concept trial are compelling, but these data have limitations due to open label treatment. However, the strong treatment effect is supported by these patients' long histories of weight gain and hyperphagia prior to treatment, and a strong dose response in the dose escalation phase. More importantly, the biology of this disorder has been well studied, and the clinical responses in these patients were strongly predicted by the deep understanding of the role of the MC4 pathway in appetite and weight regulation. The interruption of treatment effectively allowed the first patient to serve as her own control, demonstrating an immediate and rapid increase in hunger and weight after a short-term treatment withdrawal, and a rapid response to re-treatment, thereby further demonstrating the strong effect of setmelanotide. The greater than two years of treatment of our first patient, and the greater than one year of treatment for our second patient also support the ability of setmelanotide to be effective for longer treatment periods. Finally, our data supports that this indication will require chronic treatment.

Most importantly, this initial proof of concept data provides support for the belief that setmelanotide will restore activity in patients with upstream defects in the MC4 pathway, by helping patients lose weight and reduce hyperphagia. This was further supported by our other proof of concept results in MC4 pathway rare genetic obesities, such as LepR deficiency obesity, Bardet-Biedl syndrome, and Alström syndrome. Similarly, we would expect efficacy in other upstream MC4 pathway genetic disorders, others of which are under study in Phase 2 proof of concept trials.

Phase 3 Clinical Development in POMC Deficiency Obesity

After discussions with the FDA as part of our Breakthrough Therapy designation, we initiated our Phase 3 trial in POMC deficiency obesity in January 2017, Study RM-493-012. This is an open label, one-year trial, including a double-blind placebo-controlled withdrawal period, of setmelanotide in POMC deficiency obesity. This pivotal trial is assessing long-term efficacy of setmelanotide given once daily by SC injection. The trial begins with an initial period of dose titration lasting between two and 12 weeks where the individual patient's therapeutic dose will be established by upwards dose titration in two-week intervals. Thereafter, patients will continue on active treatment at their individually titrated optimal therapeutic dose for an additional 10 weeks, for a total combined dosing duration of 12 weeks at the individual patient's therapeutic dose. Patients who demonstrate at least five kilograms weight loss at the end of the open label treatment period will continue onto the double-blind, variably-timed, placebo-controlled, withdrawal period lasting eight weeks inclusive of a four-week period of placebo treatment. Following the withdrawal period, all patients will complete an additional period of setmelanotide treatment to bring the total therapeutic dosing period to approximately one year.

Based on discussions with the FDA, we plan to file an NDA with the FDA based on approximately one-year data from a pivotal cohort of 10 patients in this trial. We also plan to enroll supplemental patients who may not complete one year of treatment at the time of NDA filing, including patients between six and eleven years of age under the implementation of a pediatric amendment, to provide additional important data regarding the use of setmelanotide in people living with POMC deficiency obesity. The primary endpoint of the trial will be a categorical analysis of responders for weight, defined as patients achieving a 10% change from baseline, with mean percentage change in weight from baseline as the key secondary endpoint. Hunger-related endpoints are also key secondary endpoints in the study. Other secondary endpoints are safety and tolerability, change in body fat mass and glucose parameters, and the effect of withdrawal of setmelanotide in the double-blind, placebo controlled period. We have also obtained Scientific Advice from the European Medicines Agency, or EMA, in relation to the protocol for this trial, which is currently enrolling in the United States, United Kingdom, Germany, France, and Belgium.

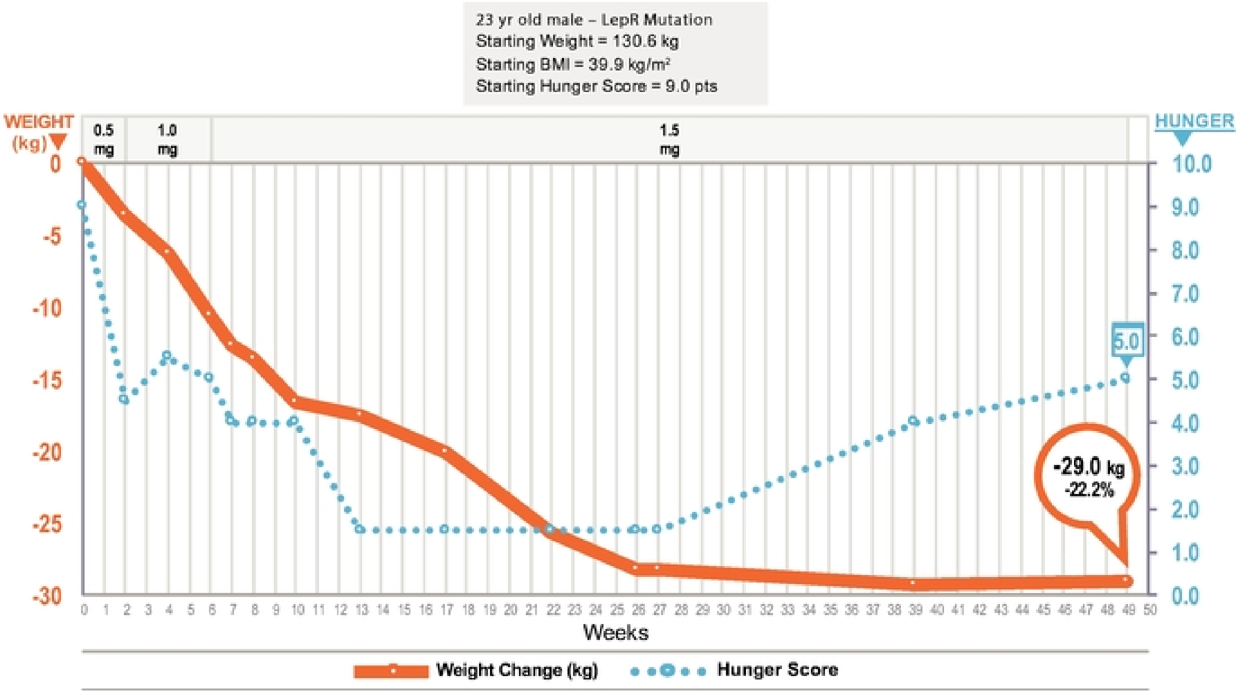
We have completed enrollment of the pivotal cohort in June 2018 and we expect to report initial Phase 3 data from this pivotal trial in the third quarter of 2019.

Phase 2 Clinical Development in LepR Deficiency Obesity

Leptin's role in obesity has been elucidated by characterization of severely obese people with homozygous mutations that impair the activity of leptin, including disruption of signaling at the LepR, known as LepR deficiency obesity. To study setmelanotide in this indication we initially amended our Phase 2 clinical trial in POMC deficiency obesity, Study RM-493-011, to also include this new and related genetically defined population of severely obese patients. We then completed this part of the Phase 2 proof of concept, open label clinical trial in patients with LepR deficiency obesity by treating three patients in this trial, who demonstrated weight loss and hunger reduction as outlined below. The results of this trial were published in May 2018 in Nature Medicine, which we believe validates the scientific and clinical importance of our Phase 2 findings.

Results from treatment with setmelanotide in these three LepR deficiency obesity patients are available. The first LepR deficiency obesity patient was a 23-year-old male, who experienced early onset of obesity and hyperphagia. After little success in controlling his weight, he underwent, and failed, a gastric banding procedure, and had regained over 20 kg in the last year since his procedure. Ahead of our trial, the patient's self-reported trial hunger score was nine out of 10 points, representing extreme hunger, and his weight and BMI at trial entry were 130.6 kg, or 287.9 lbs., and 39.9 kg/m^2, respectively. After initiation and upwards dose titration over 13 weeks of setmelanotide treatment, the patient demonstrated prompt and striking reductions in appetite and body weight with a total loss of 17.5 kg body weight, representing 13.4% of his initial body weight. Hunger scores decreased from nine points at baseline to one to two points at 13 weeks. With continued treatment for 26 weeks, the patient lost 28.2 kg, or 62.2 lbs., representing 21.6% of his initial body weight, and during that interval, he had a hunger score of one to two. Subsequently, on this dose, his weight has remained stable over an additional 35 weeks, with total weight loss of 25.1 kg or 55.3 lbs., representing 19.2% of his initial body weight over the 61 weeks of treatment. The weight loss was predominantly caused by a reduction in body fat and resting energy expenditure stayed stable during this period. This patient also had pre-trial insulin levels that were elevated as examined by an oral glucose tolerance test, as were glucose values, demonstrating insulin resistance. These values improved with setmelanotide treatment. Notably, there was also an improvement in the patient's lipid profile over 13 weeks of setmelanotide treatment. Setmelanotide was generally well tolerated in this LepR deficiency obesity trial.

The Clinical Course of our Initial Patient in the Setmelanotide LepR Deficiency Obesity Phase 2 Trial through Week 49(1)



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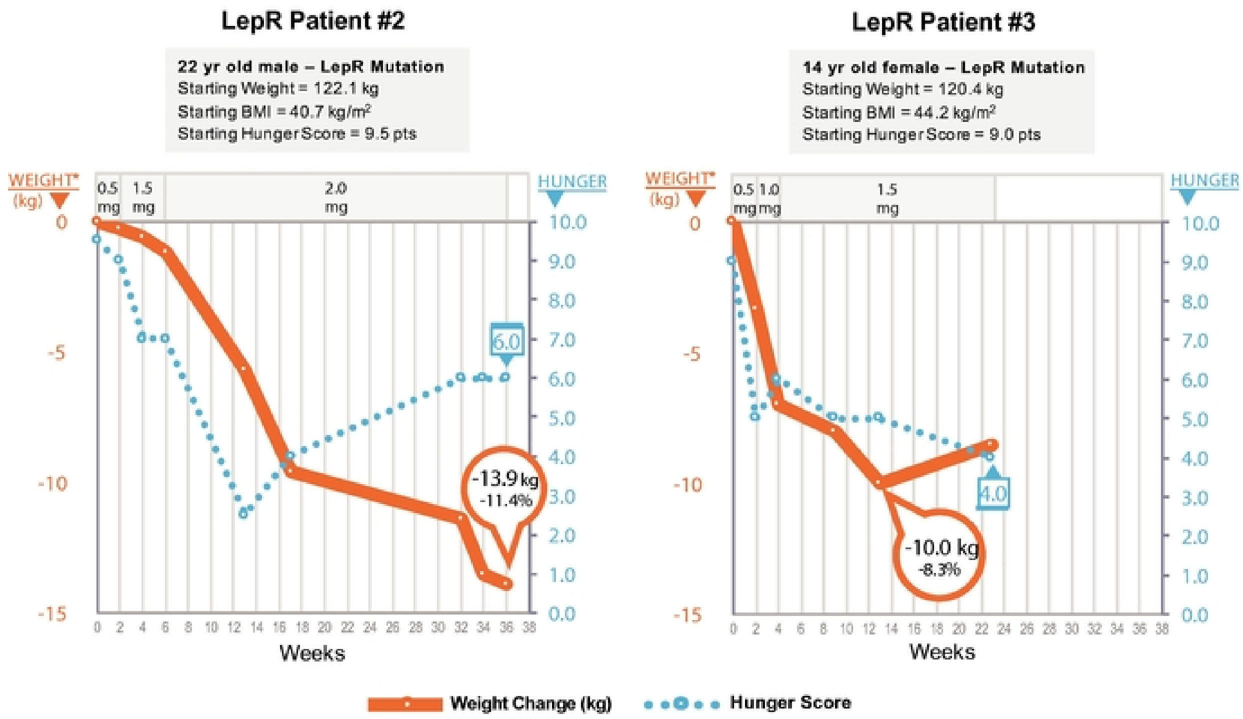
* Figures represent cumulative weight loss in kgs through approximately 49 weeks of treatment. See text for additional details.
(1) Daily setmelanotide dose adjustments over time are indicated at the top of the panel.

The second LepR deficiency obesity patient is a 22-year-old male who also experienced early onset of obesity and hyperphagia. His growth curve since infancy demonstrated early onset, severe obesity that had continued through his whole life, with little ability to control his weight gain. Ahead of our trial, the patient's self-reported trial hunger score was nine to 10 out of 10 points, and his weight and BMI at trial entry were 122.1 kg, or 269.2 lbs., and 40.7 kg/m^2, respectively. He was treated with setmelanotide and his dose was escalated up to 1.5 mg once daily with only modest effects on weight and hunger scores. However, when he was advanced to 2 mg once daily, he demonstrated prompt and striking reductions in appetite and body weight. After 17 weeks, including 11 weeks on his therapeutic dose of 2 mg/day, he had lost 9.6 kg, or 21.2 lbs., representing 7.9% of his body weight, and his hunger score dropped to two to three points. By 36 weeks of total treatment, he had lost 13.9 kg, or 30.6 lbs., representing 11.4% of his body weight. Despite good tolerance of treatment and this marked weight loss, the patient still felt dissatisfaction at the rate of weight loss and independently discontinued his setmelanotide administration for approximately 2 weeks. During this time, he regained 5.2 kg or 11.5 lbs., and his hunger score increased to nine out of 10 points, or severe hunger. The patient reported that he felt hungry every hour, and was struggling to control his appetite. As a result, treatment was re-initiated at the 2 mg dose, and was then increased to 2.5 mg per day with the goal of accelerating his weight loss. As a result, he demonstrated a significant reduction in hunger, with his hunger score decreasing from nine to two out of ten points, and in body weight. The patient remains on treatment with good tolerability.

This patient had few metabolic abnormalities at baseline, but he was hyperinsulinemic as examined by an oral glucose tolerance test. After 13 weeks of treatment, the hyperinsulinemia started to improve and the blood glucose levels during the oral glucose tolerance test normalized.

Our Second and Third Patients in the Setmelanotide LepR Deficiency Obesity Phase 2 Trial(1)



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* Figures represent cumulative weight loss in kgs; further details are in the text.
* Figures show patient data only during weeks in which patients were in compliance with the trial protocol.
(1) Daily setmelanotide dose adjustments over time are indicated at the top of the panel.

The third LepR deficiency obesity patient is a 14-year-old female adolescent, and the first adolescent patient treated with setmelanotide. Her growth curve since infancy demonstrated early onset, severe obesity her whole life, with little ability to control her weight gain. Ahead of our trial, the patient's self-reported trial hunger score was nine out of 10 points, and her weight and BMI at trial entry were 120.4 kg, or 265.4 lbs., and 44.2 kg/m^2, respectively. The patient lost 10 kg, or 22 lbs., representing 8.3% of her body weight, and her hunger score reduced to five out of 10 points in the first 13 weeks on a dose of 1.5 mg per day. Before and during treatment, the patient exhibited behavior that compromised compliance with the treatment regimen. This manifested as a misunderstanding that led her to perform the injections late in the afternoon and at an incorrect, lower dosage of 1.0 mg setmelanotide. Considering that we have noted a dose threshold for therapeutic benefit and SC setmelanotide injections have a 10- to 12-hour half-life, we concluded that the combination of a lower dose and the occurrence of the highest drug concentration at night most likely precipitated an interval of weight regain. In support of this explanation, her feeling of hunger was reduced during the night but started to increase during the day. Eventually, these errors were reported and corrected. Following such correction, careful monitoring was instituted to ensure that the patient performed the injections in the morning as instructed, leading again to reduced hunger.

This trial provides the second proof of concept for the effectiveness of setmelanotide in patients with upstream defects in the MC4 pathway, showing marked weight reduction and decreases in hunger in patients with LepR deficiency obesity. In addition, the efficacy of the drug correlates well with periods of setmelanotide treatment and withdrawal, as in POMC deficiency obesity. Based on this proof of concept for the compelling efficacy of setmelanotide in this disorder, and the FDA granting of Breakthrough Therapy designation, we transitioned the LepR development program to Phase 3.

Phase 3 Clinical Development in LepR Deficiency Obesity

Our LepR deficiency obesity development program is now in Phase 3. We have completed enrollment of the 10 patients in the pivotal cohort in the second quarter of 2018 and we expect to report initial Phase 3 data from this pivotal trial in the third quarter of 2019. This is an open label, one-year trial, including a double-blind placebo-controlled withdrawal period, of setmelanotide in LepR deficiency obesity. This pivotal trial will assess long-term efficacy of setmelanotide given once daily by SC injection in LepR deficiency obesity, and is planned to be of very similar design to the Phase 3 ongoing trial in POMC deficiency obesity. The trial begins with an initial period of dose titration lasting between two and 12 weeks where the individual patient's therapeutic dose will be established by upwards dose titration in two-week intervals. Thereafter, patients continue on active treatment at their individually titrated optimal therapeutic dose for an additional 10 weeks, for a total combined dosing duration of 12 weeks at the individual patient's therapeutic dose. Patients who demonstrate at least five kilograms weight loss at the end of the open label treatment period will continue onto the double-blind, variably-timed, placebo-controlled, withdrawal period. Following the withdrawal period, all patients will complete an additional period of setmelanotide treatment to bring the total therapeutic dosing period to approximately one year.

We have completed enrollment of the pivotal cohort of 10 patients in this trial, aged 12 years and older. We also plan to enroll supplemental patients, who may not complete one year of treatment at the time of NDA filing, including patients between six and eleven years of age under the implementation of a pediatric amendment, to provide additional important data regarding the use of setmelanotide in people living with LepR deficiency obesity.

Completion of enrollment for the pivotal cohort in this Phase 3 trial was contemporaneous with completion of enrollment for our POMC deficiency obesity pivotal trial, and so we are planning to file an NDA for each of these indications concurrently.

The primary and key secondary endpoints will be identical to those for our POMC deficiency obesity pivotal trial. This trial is currently being conducted in the United States, the United Kingdom, France, Netherlands, and Germany. Based on the FDA granting Breakthrough Therapy designation for the treatment of obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway, which includes the LepR deficiency obesity indication, we believe we can seek indications for this type of obesity with a faster path to approval, as compared to typical obesity drug candidates, because of the high unmet need and rare prevalence of this disorder.

Phase 2 Clinical Development in Bardet-Biedl Syndrome

Bardet-Biedl syndrome is a life-threatening, orphan disease with prevalence of approximately one in 100,000 in North America. We estimate that the addressable patient population for Bardet-Biedl syndrome is approximately 1,500 to 2,500 patients in the United States. It is a rare monogenic disorder that causes severe obesity and hyperphagia as well as vision loss, polydactyly, kidney abnormalities, and other signs and symptoms. Bardet-Biedl syndrome is part of a class of disorders called ciliopathies, or disorders associated with the impairment of cilia function in cells. Cilia are hair-like cellular projections that play a fundamental role in the regulation of several biological processes, including satiety signaling. Cilia dysfunction is thought to contribute to hyperphagia and obesity in Bardet-Biedl syndrome. Bardet-Biedl syndrome is a genetically heterogeneous disease that is caused by as many as 21 separate Bardet-Biedl loci defects resulting in a similar syndrome, though each Bardet-Biedl syndrome patient only has one of these defects.

The role of abnormal cilia development and function in obesity has been elucidated in animal models, most strongly for Bardet-Biedl syndrome. Studies in mouse models of Bardet-Biedl syndrome show that deficiencies in the MC4 pathway contribute to the obesity and hyperphagia in Bardet-Biedl syndrome, with animals developing hyperphagic tendencies early in life. Notably, these mice have decreased leptin receptor signaling, with the essential hallmarks of failure to activate POMC neurons. This is supported in Bardet-Biedl syndrome rodent models, where the mice respond to an MC4 agonist resulting in reduced food intake and body weight. The relation of Bardet-Biedl syndrome gene mutations to the MC4 pathway is supported by clinical data. Patients with Bardet-Biedl syndrome have higher leptin than expected for their degree of adiposity, or leptin resistance, which is consistent with the notion that ciliopathy-induced leptin signaling dysfunction is associated with leptin resistance.

Overall, these data support that the phenotypes of these ciliopathies, while complex with additional clinically important features along with obesity and hyperphagia, may be responsive to setmelanotide treatment, and will be investigated in our proof of concept Phase 2 trial.

We are studying Bardet-Biedl syndrome patients who are severely obese, and have provided proof of concept that Bardet-Biedl syndrome patients will also demonstrate decreased hunger and significant weight loss, similar to that seen in patients with POMC deficiency obesity, or LepR deficiency obesity. We have enrolled the first five patients in this trial, have reported preliminary results for these patients in a presentation at the Obesity Week 2017 meeting, and updated the clinical status of these patients in June 2018. In the second quarter of 2018, the FDA agreed to include Bardet-Biedl syndrome under our existing Breakthrough Therapy designation for setmelanotide. We are having ongoing discussions with the FDA regarding a Phase 3 trial and plan to initiate this trial and to enroll patients before the end of 2018. The FDA has preliminarily indicated that this Phase 3 trial will include both Bardet-Biedl syndrome and Alström syndrome patients.

For the Phase 2 trial, additional assessments of hunger using daily hunger scores and questionnaires were also obtained. We are using these new assessments in all our ongoing Phase 2 and Phase 3 trials and for future trials. These new assessments are as follows:

- Daily Hunger Scores. In addition to our morning assessment of hunger, as performed in the Phase 2 trials in POMC deficiency obesity and LepR deficiency obesity, we are also obtaining a daily hunger score rating in response to the question: "In the last 24 hours, how hungry did you feel when you were the *most* hungry?" Patients are asked to give a response that is measured on a scale of 0-10, whereby 0 points signifies "not hungry at all" and 10 points indicates the patient feels his or her "hungriest possible."

- Questionnaires. For patients 16 years of age and younger, we are using two observer related questionnaires as exploratory endpoints. These questionnaires are completed by the patient's parent or other caregiver.

  - The Food Problem Diary, or FPD, is based on food-related behaviors. This questionnaire was adapted from a similar questionnaire that was used with patients with Prader-Willi syndrome. The questionnaire is rated on a 30-point scale where 30 points is strong evidence of hyperphagia and 0 points is evidence of no hyperphagia. The best possible response therefore is 0 points.

  - The Significant Event Questionnaire, or SEQ, counts events not typically seen in this population, such as a patient leaving food on his or her plate at a meal. This questionnaire consists of eight "yes" or "no" questions. The best possible response is 8 points, since this questionnaire tracks events and behavior not typically seen in patients with MC4 pathway disorders. In contrast with other score scales, a higher score in this hunger assessment category represents improvement, and thus, the results are plotted in reverse scale and downward trends indicate improvement.

We believe that proof of concept in Bardet-Biedl syndrome has been demonstrated by improvements in hunger and weight reduction, supporting that this is a setmelanotide-responsive, MC4 pathway disorder. The age of the patients ranged from 12 to 61 years of age. The starting weights of the patients ranged from 98.3 to 147.5 kg and BMI ranged from 42 to 49. The starting hunger scores for the adult patients ranged from 6 to 9 points on the 10-point scale, with higher scores indicating more hunger and the SEQ scores for the two adolescent patients were both 1.

Description of the Five Bardet-Biedl patients in the Phase 2 Proof of Concept study

Patient Number	Age (yrs)	Bardet-Biedl Type	Starting Weight (kg)	Starting BMI	Starting Hunger Score
1	25	1	147.5	44	Most hungry score = 9
2	61	2	99.4	44	Most hungry score = 7
3	16	10	121.6	44	FPD = 6/SEQ = 1
4	17	12	98.3	42	Most hungry score = 6
5	12	1	119.3	49	FDP = 15/SEQ = 1

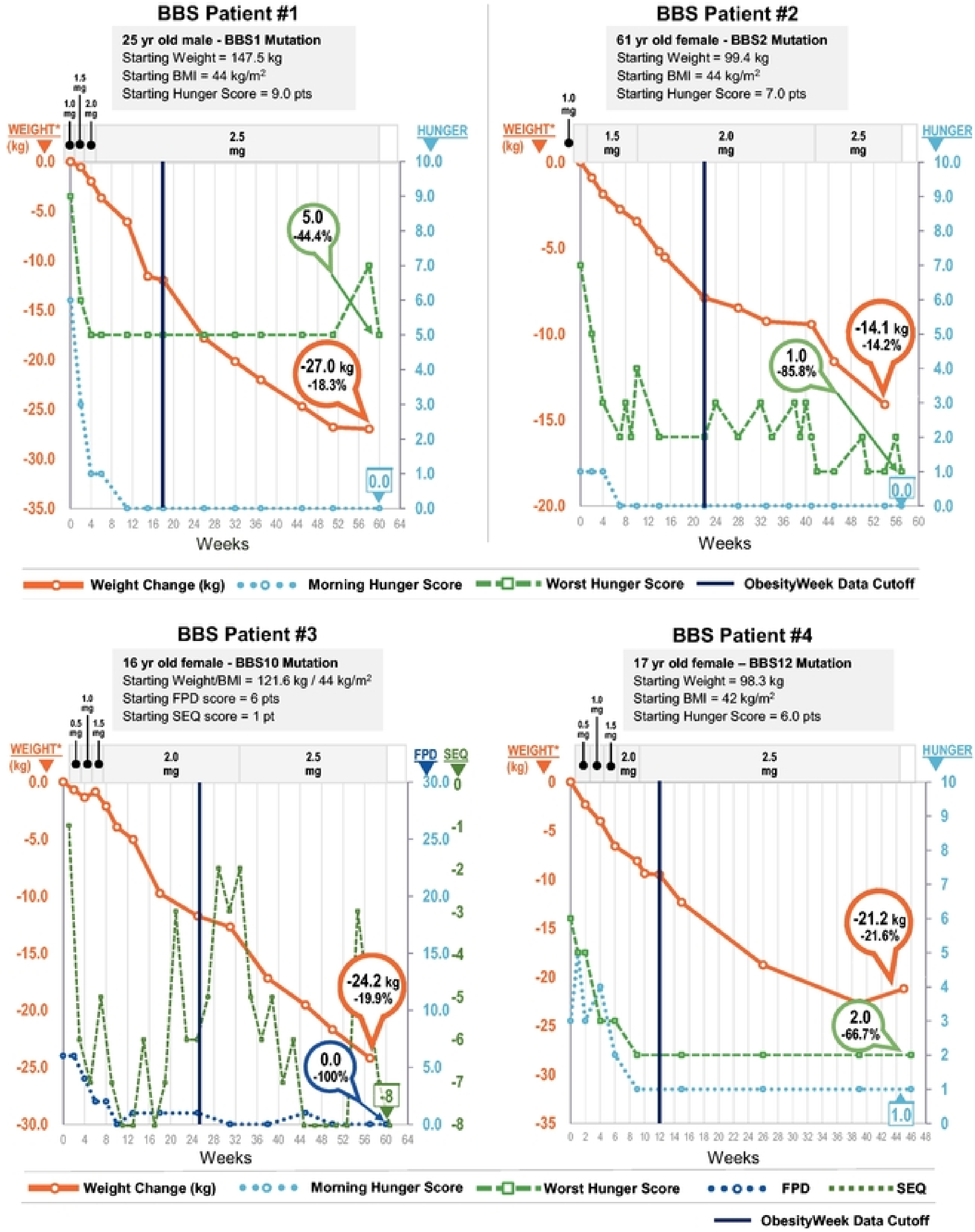
Two patients with Bardet-Biedl syndrome type 1 mutations and one each with Bardet-Biedl syndrome types 2, 10 and 12 mutations were enrolled. Results for weight and hunger endpoints are depicted for four Bardet-Biedl patients demonstrating therapeutic responses to setmelanotide. Total treatment durations now lasting between 46 and 60 weeks, with up to 14 weeks, and in one case up to 42 weeks, representing time spent in the dose titration period designed to define an individualized therapeutic dose. Four of the five patients showed clinically important, marked weight loss of 27.0 kg, 14.1 kg, 24.2 kg, and 21.2 kg, or 59.5 lbs., 31.1 lbs., 53.4 lbs., and 46.7 lbs. respectively, and a decrease of 18.3%, 14.2%, 19.9%, and 21.6%, respectively. Hunger scores were reduced by 44.4%, 85.7%, 100.0%, and 66.7%, respectively, in these four patients. This data is summarized below.

Summary of the Phase 2 data for Our Four Patients in the Setmelanotide Bardet-Biedl Syndrome Phase 2 Trial who showed improvements in both weight and hunger

Bardet-Biedl Patient Number	Weight loss (kg)	Weight loss (lbs)	Weight loss (%)	Decrease in hunger score (%)
1	27.0	59.5	18.3%	44.4%
2	14.1	31.1	14.2%	85.7%
3	24.2	53.4	19.9%	100.0%
4	21.2	46.7	21.6%	66.7%
Mean	**21.6 kg**	**47.7 lbs**	**18.5%**	**74.2%**

For these four Bardet-Biedl syndrome patients who responded to treatment with setmelanotide, mean weight loss reached 18.5% of body weight, and mean hunger decreased to 74.2%. The time course of response for the individual patient weight loss and hunger scores are shown below.

Our Four Patients in the Setmelanotide Bardet-Biedl syndrome Phase 2 Trial who showed improvements in both weight and hunger(1)(2)(3)



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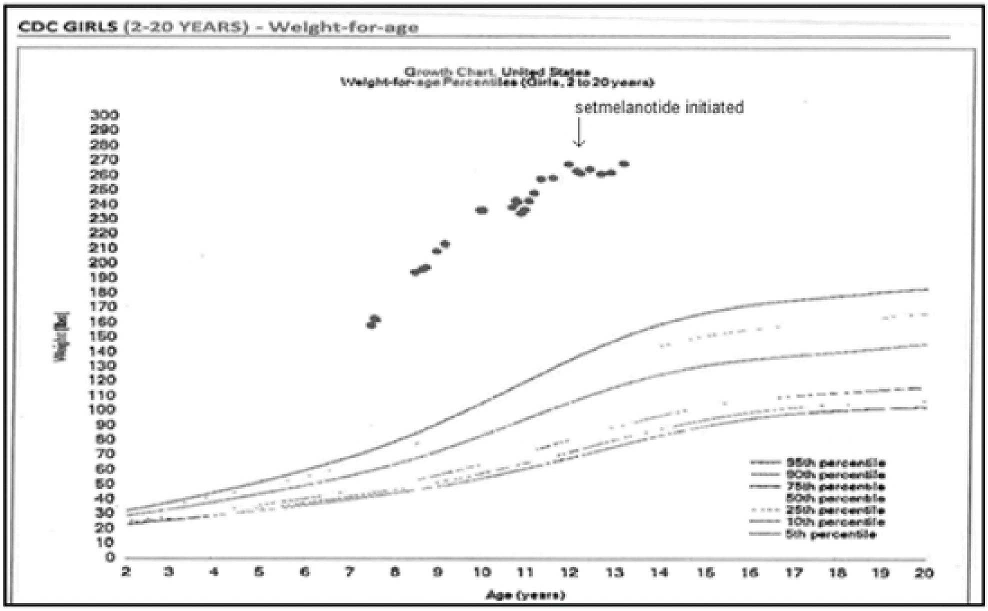
* Figures represent cumulative weight lost in kgs

FPD: Food Problem Diary; Score Range 0 to 30, higher score means worse result

SEQ: Significant Event Questionnaire, which counts significant food behavior events rarely seen in this population (Y/N for 8 behaviors), so maximum score of 8 points means greatest improvement. Shown in reverse scale so downward movement equals improvement for clarity.

(1) Daily setmelanotide dose adjustments over time are indicated at the top of the panel.
(2) In some cases, dates for entry of weight and hunger assessment data may differ within a single patient.
(3) For Bardet-Biedl syndrome and Alström syndrome patients, data as of May 27, 2018.

The fifth patient, a patient with a Bardet-Biedl syndrome type 1 mutation, showed marked improvement in hunger scores with a 53.3% decrease, but did not demonstrate any body weight change after 33 weeks on treatment, including a final 12-week test period on 3.0 mg daily. However, the weight curve for this patient indicated a slowing of prior childhood weight gain upon treatment with setmelanotide, as indicated with an arrow in her pediatric growth chart, below. This patient was a 12-year-old with Type 1 diabetes who entered the trial with extremely poor glucose control, with an average blood sugar level, or HbA1c, of 10.1%. We have been investigating the reason for the inconsistency between her improvement in hunger and lack of weight loss. During her treatment, her HbA1c showed an improvement to 7.6%. Setmelanotide was generally well tolerated in all patients in this Bardet-Biedl syndrome Phase 2 proof of concept study.



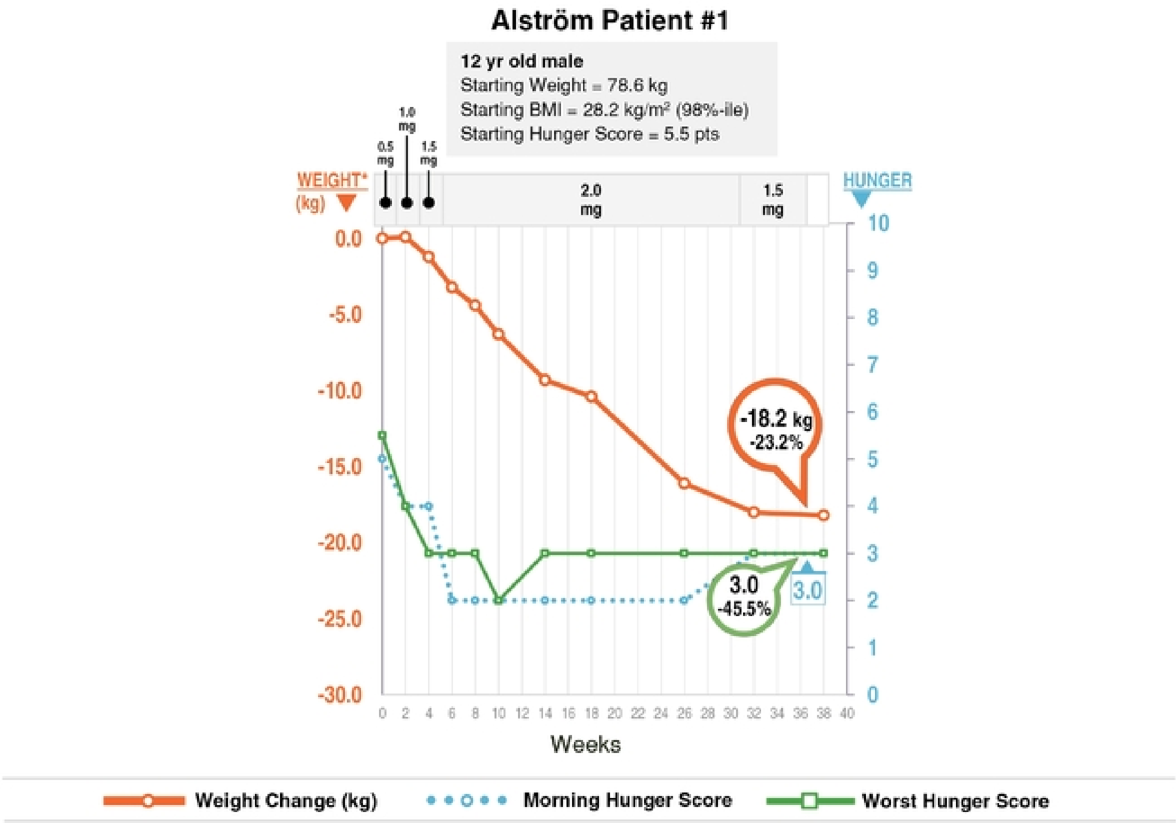
Four additional Bardet-Biedl patients (3 adolescents, 1 adult) have been enrolled in this Phase 2 study, all of whom have been treated for short duration and/or are still in the titration phase, including patients with two additional Bardet-Biedl syndrome types. In addition, one of these patients, an adolescent who had syndromic Bardet-Biedl syndrome, was diagnosed by clinical presentation but had no genetic abnormalities in any Bardet-Biedl syndrome gene. Two of these patients are showing promising responses in weight loss and hunger. The third patient, diagnosed by clinical presentation only, is too early to determine. The fourth patient did not show improvements in either weight or hunger and was discontinued.

Phase 2 Proof of Concept Study of Patients with Alström Syndrome

We are conducting a Phase 2, proof of concept trial in Alström syndrome, which is a life-threatening, ultra-rare orphan disease with a prevalence of approximately one in 1,000,000 in North America and we estimate that the addressable patient population for Alström syndrome obesity is approximately 500 to 1,000 patients worldwide. Alström syndrome shares many clinical features with Bardet-Biedl syndrome, including obesity and hyperphagia, and is also characterized by progressive vision loss, deafness, congestive heart failure, hyperinsulinemia and type 2 diabetes mellitus. Similarly, Alström syndrome is a ciliopathy caused by mutations in the ALMS1 gene, which has also been shown to be important for cilia function. Like Bardet-Biedl syndrome, recent scientific studies identify genetic deficiencies affecting the MC4 signaling pathway as a potential cause of the obesity and hyperphagia associated with Alström syndrome. Studies in a mouse model of Alström syndrome show a reduction in the number of cilia in specific neurons in the hypothalamus that are critical for MC4 pathway signaling. While Alström syndrome is less well studied than Bardet-Biedl syndrome, the similar pathophysiology of cilial dysfunction and clinical presentation support that deficiencies in the MC4 pathway are implicated in the obesity and hyperphagia observed in Alström syndrome. Therefore, we hypothesize that setmelanotide treatment can be applied to treat Alström syndrome.

We are studying Alström syndrome patients who are severely obese. We believe, our initial proof of concept data, shown below, demonstrates that Alström syndrome patients may also experience decreased hunger and significant weight loss similar to that seen in patients with POMC deficiency obesity, LepR deficiency obesity, or Bardet-Biedl syndrome. We have enrolled patients in this trial and have updated the clinical status of these patients in June 2018. The FDA has also recently included Alström syndrome under our existing Breakthrough Therapy designation. As mentioned for Bardet-Biedl syndrome, we are having ongoing discussions with the FDA regarding a Phase 3 trial and plan to initiate this trial and to enroll patients before the end of 2018. The FDA has preliminarily indicated that this Phase 3 trial will include both Bardet-Biedl syndrome and Alström syndrome patients.

The initial Alström syndrome patient in our Phase 2 clinical trial was a 12-year-old male, starting weight of 78.6 kg, or 173.2 lbs., with a BMI of 28.2 kg/m^2 (above the 98th percentile for his age). At baseline, his initial "worst hunger" score was 5.5 points, and his morning hunger score was 5 points. This patient has been treated for 38 weeks including titration, most of that time on a dose of 2 mg/day. During the course of 38 weeks of treatment, he experienced weight loss of 18.2 kg, or 40.1 lbs., which represented a 23.2% weight loss and a 45.5% decrease in hunger. Clinical assessment by the Dykens hyperphagia questionnaire, another instrument also collected in this patient only, demonstrated a baseline of 31 out of 55 possible points, which improved to 11 points, or a 64.5% improvement in hyperphagia. Because his body weight was approaching ideal body weight, and he is a growing child, his dose was reduced to 1.5 mg/day, with stabilization of his weight.



Three additional Alström patients (2 adolescents, 1 adult) have been enrolled in this Phase 2 study, all of whom have been treated for short duration and/or are still in the titration phase. One of these patients is showing promising responses in weight loss and hunger, one is too early to determine, but one patient, the adult, did not show improvements in either weight or hunger and was discontinued.

Phase 3 Clinical Development in Bardet-Biedl and Alström Syndrome

Since the FDA agreed to include Bardet-Biedl syndrome and Alström syndrome under our Breakthrough Therapy designation, we have begun in May 2018 an ongoing discussion about Phase 3 trial design with the FDA, and have received preliminary guidance on many aspects of the Phase 3 development programs in Bardet-Biedl syndrome and Alström syndrome. Based on these discussions, we are planning a combined Phase 3 study to include both Bardet-Biedl and Alström patients in a single Phase 3 trial, including at least 20 Bardet-Biedl syndrome patients and at least 6 Alström syndrome patients, aged 6 years and older. The combined trial is likely to lead to a more rapid path for approval of these two indications than two separate trials. Like previous setmelanotide Phase 3 trials in POMC and LepR deficiency obesities, we are planning an open label, approximately one-year trial, assessing long term efficacy of setmelanotide given once daily by SC injection. We may also plan to enroll supplemental patients who may not complete one year of treatment at the time of NDA filing. We expect to discuss with the FDA the primary endpoint of the trial. Potential endpoints will likely include a categorical analysis of responders for weight, with mean percentage change in weight from baseline as a key secondary endpoint. Hunger-related endpoints are also likely to be key secondary endpoints in the study.

We are planning the trial to begin with an initial period of dose titration, using a simplified titration scheme over 2 weeks for adults, and possibly slightly longer for pediatric patients. This trial may include a short, 12-week, randomized, placebo-controlled period. Following the 12-week, double-blind, placebo controlled period, all patients will complete an additional period of active setmelanotide treatment to complete the approximately one-year trial. We are also discussing with the FDA a potential alternative primary endpoint for growing pediatric patients that will capture the therapeutic benefits of setmelanotide in the pediatric population.

We plan to continue ongoing discussion with the FDA, complete the Phase 3 protocol, initiate the Phase 3 study and enroll our first patients by the end of 2018. It is anticipated that this study will be conducted in both the United States and Europe.

Phase 2 Proof of Concept Studies Focused on Patients with Monogenic Disorders of the MC4 Pathway: Heterozygous Mutations in the MC4 Pathway and Epigenetic Disorders of the MC4 Pathway

We are conducting Phase 2, proof of concept trials in a variety of monogenic, upstream disorders of the MC4 pathway, including POMC and other MC4 pathway gene heterozygous mutations, and epigenetic disorders of the MC4 pathway. These trials are Phase 2 open label, single arm, proof of concept trials assessing the effect of setmelanotide on the rare genetic disorders of obesity described below. We hypothesize that these disorders may be genetically-defined deficiencies upstream in the MC4 pathway. Each trial includes a three-month proof of concept phase at which weight loss, hunger and other metabolic parameters will be evaluated. If patients demonstrate significant weight loss and acceptable safety and tolerability, they will continue treatment for evaluation of setmelanotide's effects for a total of one year. Similar to our previous trials, this trial begins with an initial period of dose titration where the individual patient's therapeutic dose is established by upwards dose titration in two week intervals. We plan to enroll from 20 up to 100 patients between these two rare genetic populations. We are conducting these trials, as we did for the ongoing Bardet-Biedl syndrome and Alström syndrome Phase 2 trial described above, under basket protocols, which are designed to capture a broad range of patient populations to be treated under one investigational protocol. We believe this approach is efficient for studying many potential indications, and we intend to add additional populations to these basket protocols over the next one to two years.

The genetic disorders we are studying in our additional Phase 2 proof of concept trials are outlined below, and initial, preliminary Phase 2 data for each indication is summarized.

a. Clinical Development in MC4 Pathway Heterozygous Deficiency Obesity

MC4 pathway heterozygous deficiency obesity is caused by the loss of one of the two genetic copies of either the genes for POMC, PCSK, LepR, or other genes in the MC4 pathway. Animal models support that such heterozygous deficiency in the critical leptin-melanocortin pathway can result in a strong predisposition to severe obesity. The effect of genetic heterozygous deficiency obesity was first demonstrated for another gene in the MC4 pathway: MC4R heterozygous deficiency obesity. Later data also supported that POMC heterozygous deficiency obesity also results in a strong predisposition to obesity, though the epidemiology and clinical characterization of these patients is less well known. An estimated 2% of severe, early onset obesity patients have POMC heterozygous deficiency obesity, which is much more common than the ultra-rare POMC deficiency obesity in which both copies of either the POMC or PCSK genes are impaired. Our initial clinical focus is on the most severely obese MC4 pathway heterozygous patients to test the hypothesis that severely obese heterozygous POMC patients might also respond substantially to setmelanotide treatment.

We are studying patients who are severely obese, or whose BMI is equal to or greater than $40kg/m^2$, and who are heterozygous deficient for POMC, LepR, or other genes in the MC4 pathway. These patients have a heterozygous genetic mutation resulting in full or partial loss of MC4 pathway signaling to the downstream MC4R. The purpose of studying these patients in this trial is to provide proof of concept that severely impaired MC4 pathway heterozygous deficiency obesity patients will also demonstrate significant weight loss, similar to though possibly of less magnitude, as that seen in patients with POMC deficiency obesity or LepR deficiency obesity. We are enrolling this trial at sites in the United States and Europe, and reported initial, preliminary results in June 2018.

Five heterozygous patients have been enrolled, mostly for short durations, in this Phase 2 trial. The longest treated patient, on treatment for 34 weeks including titration, is showing promising responses in weight loss of 23.1 kg, or 50.9 lbs. which represented a 15.4% decrease in body weight, and also showed an 80% decrease in hunger score. A second patient has shown 9.5 kg, or 21.0 lbs. of weight loss, which represented a 6.5% decrease in body weight, and also showed a moderate 20% decrease in hunger score. One patient did not show improvements in either weight or hunger and was discontinued due to lack of efficacy, and two patients discontinued early due to tolerability issues related to muscle cramps or tanning, respectively. Four of the five patients treated to date were enrolled at a single site. We are currently opening a number of additional sites with relevant pre-identified heterozygous patients in their databases.

POMC heterozygous deficiency obesity is complex in many ways, in that there appears to be variable penetrance, or manifestation of heterozygous mutations. As a result, we intend to study a larger number of heterozygous patients in Phase 2, to more carefully delineate those patients most debilitated and those who will have the best response to setmelanotide, before we discuss the design for a Phase 3 study with the FDA. We intend to provide an update on a larger number of heterozygous patients in the first quarter of 2019.

Mutations that are of particular interest include mutations to the section of the POMC gene that are translated into the protein, beta-melanocyte stimulating hormone, or b-MSH. These mutations have been implicated in human and canine obesity. In 2002, researchers identified one specific heterozygote mutation of b-MSH, called the R236G mutation, in two children with extreme childhood obesity. This R236G mutation results in an abnormal b-MSH protein with a markedly reduced ability to activate the MC4R itself, and may also prevent other natural MC4R ligands from activating the MC4R. These combined effects may result in more significant obesity than other heterozygous mutations. The overall prevalence of this mutation is rare, 0.7% of the obese population is estimated to carry this mutation, but our genotyping study of 560 patients with early onset, childhood obesity has identified five heterozygote patients with the R236G mutation, all with severe obesity. Because, in our genotyping study and possibly in the scientific literature, this mutation is associated with severe obesity and has a relatively-high observed prevalence, this mutation will be a focus when enrolling our Phase 2 trial in POMC heterozygous obesity. We are studying patients who are heterozygous deficient for other genes in the MC4 pathway, though less is known about the epidemiology and clinical impact of these other heterozygous deficiency obesities. We have also hypothesized that patients who carry high allelic burden in this pathway, or who have genetic disorders in two or more of the genes of the MC4 pathway, and who therefore might have some impairment at more than one location in the MC4 pathway, might also be responsive to setmelanotide.

b. Clinical Development in Patients with Epigenetic Changes at the POMC receptor

In our proof of concept Phase 2 trials, we are studying patients suffering from obesity due to a partial lack of MSH due to an epigenetic POMC variant. Epigenetics changes are DNA modifications that can change gene expression without altering the DNA sequence itself. The most stable epigenetic modification is called DNA methylation. Recently, our academic collaborators in Berlin have described a POMC hypermethylation variant, which correlates with increased body weight in children and adults. Therefore, the presence of the POMC genetic/epigenetic variant leads to an increased risk for obesity based on reduced POMC gene activity. We expect that these patients under express the POMC gene product and as a result have a partial MSH deficiency.

There is convincing evidence that such epigenetic variants are potentially major factors for an increased individual risk to develop obesity later in life, and we hypothesize that the most obese patients in their populations may benefit from treatment with setmelanotide. However, epigenetic variation is likely not the only reason for the development of obesity in this patient group, because these variants are also observed in normal weight individuals, although to a lesser extent. At this point, no epidemiology data is available to estimate the size of the POMC epigenetic deficiency obese population.

We are studying patients who are severely obese, or whose BMI is equal to or greater than $40kg/m^2$, and who have hypermethylation at the POMC gene. The purpose of studying these patients in this trial is to provide proof of concept that severely impaired, epigenetic POMC variant obesity patients will also demonstrate significant weight loss similar to, though possibly of less magnitude, as that seen in patients with POMC deficiency obesity or LepR deficiency obesity. We are enrolling this trial at sites in the United States and Europe, and reported initial, preliminary results in June 2018.

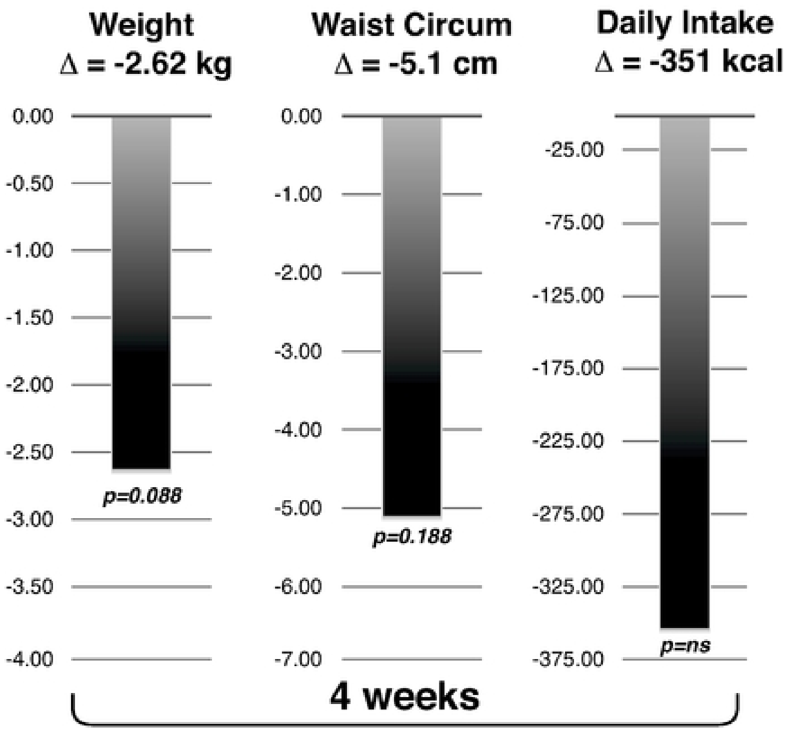
Two epigenetic patients have been enrolled, one of whom is just starting titration. The longer treated patient, on treatment for 27 weeks including titration, is a 20-year-old female, with a starting weight of 182.2 kg, or 401.7 lbs., and a BMI of 55.0 kg/m^2. Her starting hunger score was 7.5 points. As she was titrated, her hunger score decreased 60% to three points and she began to lose weight. Due to a vacation, she withdrew from treatment for approximately four weeks and her hunger score returned to baseline but she did not regain weight over that period. With resumption of treatment, her hunger score decreased to 3.5 points, and at week 27, she had lost 16.8 kg, or 37.0 lbs., which represented a loss of 9.2% of body weight.

Phase 1b Clinical Development in Patients with Heterozygous MC4R Gene Mutations

Early studies in downstream MC4 pathway defects demonstrated good efficacy and tolerability, and served as a foundation for potentially greater efficacy in upstream MC4 pathway deficiencies. We established proof of concept for efficacy of setmelanotide in patients with an MC4R heterozygous genetic mutation in one cohort of patients in our Phase 1b clinical trial. This clinical trial was a double-blind, placebo-controlled, randomized Phase 1b clinical trial designed to evaluate the effect of setmelanotide on weight loss and safety in obese patients with a heterozygous mutation of the MC4R gene. The initial cohort of eight patients was treated for four weeks with setmelanotide or placebo. The setmelanotide group showed weight loss of 3.48 kg, or 7.67 lbs., approximately 2.62 kg, or 5.78 lbs., more weight loss than the placebo group, which showed weight loss of 0.85 kg, or 1.87 lbs. Other parameters supporting weight loss were also positively impacted by setmelanotide. We believe that these results support the hypothesis that setmelanotide can be effective in weight loss in MC4R deficient patients, and provide evidence of the minimum expected treatment effect of setmelanotide, approximately 0.9 kg/week, or 1.98 lbs./week, of weight loss over four weeks, even in a situation where setmelanotide's action is on a downstream MC4 pathway that is no longer fully functional due to heterozygous MC4R mutations. However, our focus is on upstream disorders of the MC4 pathway where we hypothesize that setmelanotide can serve as replacement therapy and provide more compelling efficacy.

The following figure depicts preliminary data relating to our setmelanotide Phase 1b clinical trial in MC4 heterozygous deficiency obesity patients:

Setmelanotide Phase 1b Trial MC4 Heterozygous Patients: Placebo Subtracted Differences(1)(2)



(1) Over four weeks of treatment with setmelanotide 0.01 mg/kg/day by continuous SC infusion.
(2) Preliminary data.

In general, we consider a p-value of 0.05 to be significant. P-values are an indication of statistical significance reflecting the probability of an observation occurring due to chance alone. However, it is not possible to determine a p-value for very small sample sizes, such as one- or two-patient trials.

Other Clinical and Scientific Initiatives in Genetic Obesity

Genotyping Study

Leveraging new understanding of severe obesity caused by specific genetic defects has the potential to improve both diagnosis and treatment for specific types of life-threatening obesity. Therefore, we are sponsoring the Genetic Obesity Project, which is dedicated to improving the understanding of severe obesity that is caused by specific genetic defects—particularly rare genetic disorders that result in life-threatening obesity. As part of that initiative, we have initiated a genotyping study—the Genetic Obesity ID | Genotyping Study—in which eligible patients are genotyped for rare genetic disorders of obesity. The goal is to develop a screening algorithm for selecting patients to be genotyped and diagnosed with POMC deficiency obesity and LepR deficiency obesity, and to guide further genotyping efforts; in addition, it is our expectation that patients who can participate in our clinical trials will be genetically identified. We are currently including other MC4 pathway deficiencies in the study. Key entry criteria for the study include a history of severe, early onset obesity, along with hyperphagia and are consistent with the recently published Pediatric Obesity guidelines published by the Endocrine Society. Study investigators, who are academic experts in childhood obesity, are located in both the United States and

Europe. We plan to work with these investigators to publish the results of this study and guidance on the use of the algorithm for screening, to enable more systematic diagnoses of these rare genetic disorders of obesity. Our preliminary results in 560 genotyped patients, described below, suggest we can successfully identify these patients using our algorithms. We have now genotyped a few thousand patients and our preliminary results from these additional patients remain consistent. We are continuing our efforts to genotype patients.

Number of Patients	Percent	Genetic Defect
2	0.36%	POMC deficiency obesity (PCSK1)
3	0.54%	LepR deficiency obesity
59	10.5%	Heterozygous deficiency
5	0.89%	R236G Heterozygous deficiency

Unique Mechanism of Action of Setmelanotide at the MC4R

We recently published new molecular evidence of setmelanotide action on MC4R in Nature Medicine in May 2018, which demonstrates a unique mechanism of action compared to the endogenous activator, MSH, and first generation MC4R agonists. With agonism of the MC4R, setmelanotide appears to use different signaling pathways inside the MC4R cell, and to better compete away the natural antagonist at MC4R (AgRP). This may explain the remarkable efficacy of setmelanotide for appetite control in individuals with severe hyperphagia, and may also suggest why setmelanotide does not clinically increase blood pressure or heart rate, compared to former MC4R agonists. Further research in this area is planned as well.

Setmelanotide: Clinical Development Program in Prader-Willi Syndrome

PWS is a life threatening, orphan multigenic disease with prevalence estimates ranging from approximately one in 8,000 to one in 52,000, with at least 8,000 diagnosed patients in the United States. A hallmark of PWS is hyperphagia, leading to severe obesity and other complications. For PWS patients, hyperphagia and obesity are the greatest threats to their health, and these patients are likely to die prematurely as a result of choking, stomach rupture, or from complications caused by morbid obesity.

The genetics of PWS are complex, involving many genes on chromosome 15 that are not properly expressed. Recent discoveries highlight that a defect in one of these, the melanoma antigen family L2, or MAGEL2, gene, in rodent models impairs the function of POMC neurons, which are key components of the MC4 pathway. Studies have suggested a link between defects in MAGEL2 in some humans with obesity, hyperphagia, autism spectrum disorders, reduced intellectual ability and most other aspects of behavior and metabolism associated with PWS. However, the connection of PWS with the MC4 pathway is complex.

We have completed a Phase 2 proof of concept, double-blind, placebo-controlled, randomized clinical trial in PWS, Study RM-493-010, which enrolled 40 patients for four weeks of active setmelanotide treatment, administered once daily by SC injection. This trial was intended to assess the effects of setmelanotide on weight reduction, and PWS-specific hyperphagia-related behaviors, as PWS patients do not respond to hunger questionnaires, as well as determine its safety profile. Based on the data from this Phase 2 clinical trial, we do not believe we will be positioned to proceed directly into a Phase 3 clinical trial.

The trial included a two-week run-in period, a four-week double blind, randomized, placebo-controlled parallel group main trial, a two-week double-blind, randomized, placebo-controlled withdrawal period during which half of the trial patients were randomized to either continue to receive their therapy or be switched to the alternative therapy, from active to placebo, or vice versa, and a two-week active-treatment extension. There were four treatment arms in the trial: placebo (N=14); 0.5 mg of setmelanotide SC injection daily (N=4), 1.5 mg of setmelanotide SC injection daily (N=12), and 2.5 mg of setmelanotide SC injection daily (N=10). Patients were 17 to 54 years of age, with a mean BMI of 39.4 kg/m^2, and with a genetically confirmed diagnosis of PWS. Primary endpoints for the trial included safety and tolerability, weight loss and hyperphagia, with hyperphagia to be measured by a PWS hyperphagia observer reported outcome, or ORO, questionnaire. Secondary endpoints included dual-energy x-ray absorptiometry measurements, pharmacokinetics, effects during the randomized withdrawal stage, and effects on quality of life and food-related and other behaviors. Primary evaluations were assessed at the end of the four-week double blind parallel group stage, as well as after the withdrawal stage and open label extension.

The results of the trial showed modest effects on hyperphagia, which did not approach statistical significance, and no effect on weight, though there may have been some small evidence of clinically-important weight loss in the very small group of patients who were randomized to the highest dose of setmelanotide over the longest interval of treatment (N=4 patients, post-hoc evaluation, non-significant). There was good safety and tolerability, providing support for the 2.5 mg daily dose, with only injection site reactions common in both active and placebo groups. There were no serious adverse events, no significant safety issues or changes in labs or other safety parameters, and the one discontinuation was due to injection site reactions.

PWS is a complex multigenic disease, and the hypothesis that PWS is an upstream MC4 pathway disorder is supported primarily on the role of only one of those genes, MAGEL2, in animal models of obesity. Our results may support that PWS is not an upstream MC4 pathway disorder. Alternatively, other design factors may have influenced the outcome of this trial, and we have started initial planning for future Phase 2 trials in PWS that address these potential factors: longer duration of treatment, younger patient population, improved setmelanotide pharmacokinetics, consideration of higher doses, and operational limitations of the completed Phase 2 trial.

In addition to our plans to further evaluate setmelanotide in PWS, we also plan to pursue the development of of RM-853, our preclinical candidate GOAT inhibitor for PWS. Additionally, given setmelanotide and RM-853's distinct mechanisms of action, we plan to explore opportunities to evaluate the two compounds in combination, as we believe there may be complementary effects.

Setmelanotide Clinical Development in General Obesity Patients

Initial studies in general obesity provided preliminary evidence of efficacy and of good tolerability, and served as a foundation for the clinical development of setmelanotide. The general obese population is defined as having a BMI of equal to or greater than 30 kg/m^2. In our initial clinical trials, we delivered setmelanotide with continuous SC infusion using an insulin pump. More recently, our administration has been converted to a once daily SC injectable formulation. In addition, we have an ongoing trial to assess the pharmacokinetics of a new, long-acting formulation of setmelanotide.

The table below summarizes the setmelanotide studies that we conducted in general obese patients under IND # 112595 submitted to the Division of Metabolism and Endocrinology Products, Center for Drug Evaluation and Research, FDA.

Completed and Ongoing Setmelanotide Clinical Trials in the General Obese Population

Short Study Title	Population	Route of Administration Formulation	Number of Subjects/ Patients	Status
RM-493-001 Single Ascending Dose Trial in Healthy Obese Subjects	Obesity	Continuous infusion	36 healthy obese subjects	Completed
RM-493-002 Multiple Ascending Dose Trial in Healthy Obese Subjects	Obesity	Continuous infusion SC injection	54 healthy obese subjects	Completed
RM-493-003 A Phase 2a Weight Loss Trial in Obese Patients using Continuous Infusion	Obesity	Continuous infusion	74 healthy obese subjects	Completed
RM-493-005 Pre-screening Genetic Testing of Healthy Obese Subjects	N/A Genetic Screening Study	N/A	N/A	Completed
RM-493-006 A Phase 1b 2-Period Crossover Trial on Energy Expenditure in Obese Subjects	Energy Expenditure In Obesity	Continuous infusion	12 healthy obese subjects	Completed
RM-493-008 A Phase 1 Pharmacokinetic Trial of New Once-daily Injectable Formulations	PK/Obesity	SC injection	12 healthy obese subjects	Completed
RM-493-009 A Staged, Phase 1b/Phase 2a Pharmacokinetic/Weight Loss Trial in Obese Patients using Sub-Cutaneous Injection	Obesity	SC injection	97 healthy obese subjects	Completed
RM 493 018 A Long-Acting Formulation PK Study of RM-493	Obesity	SC injection of long-acting formulation	30 healthy obese subjects	Parts A and B completed

SC=subcutaneous.

Phase 2 Clinical Development in the General Obese Population

a. Phase 2 Clinical Trial Results with Continuous Infusion

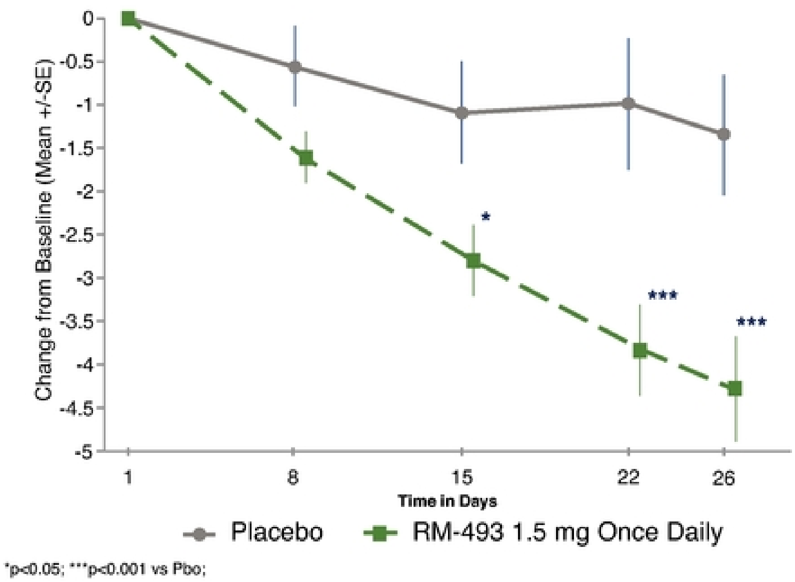
We conducted our first Phase 2 clinical trial of setmelanotide using continuous SC infusion. This was a 12-week, Phase 2 proof of concept clinical trial in general obese patients using the SC continuous infusion formulation of setmelanotide delivered by an insulin pump. We treated approximately 74 obese patients with either placebo or setmelanotide at a dose of 1.0 mg over 24 hours, with no serious adverse events or other safety indications from laboratory tests, electrocardiograms or vital signs noted in the setmelanotide treatment group. Evaluation of the pharmacokinetics, or blood levels, of setmelanotide from this clinical trial demonstrated that the SC continuous infusion method of drug administration was not optimal. A large number of patients did not meet the target pharmacokinetic exposures of setmelanotide that our Phase 1 clinical trials suggested would have to be achieved in order for setmelanotide to show efficacy. This clinical trial did not demonstrate statistically significant weight loss compared to the placebo. We believe patients in this clinical trial lacked adequate exposure to setmelanotide, and concluded that all future efficacy clinical trials in obese patients should be conducted using the SC injection method. This belief is based on a prior Phase 1 pharmacokinetic trial, which used the SC injection formulation and demonstrated higher pharmacokinetic exposures in obese patients.

b. Phase 2 Clinical Trial with Once Daily SC Injection

We conducted a three-stage, randomized, placebo-controlled, Phase 2 12-week general obesity trial, with approximately 100 obese patients, using our SC injection formulation, primarily with once daily dosing. We designed this Phase 2 clinical trial to bridge between the earlier clinical trials that used continuous infusion and all future clinical trials that use the formulation for once daily SC injection. Therefore, the primary purpose of the staged approach in this trial was to assess if appropriate pharmacokinetic targets could be reached with the new SC injection, first in an in-patient setting similar to the setting where robust weight loss was demonstrated in the Phase 1 general obesity trial, and then in an outpatient setting.

Overall, setmelanotide demonstrated significant weight loss over 12-weeks in all stages, with placebo subtracted weight loss, or the difference in the amount of weight gained or lost in the active treatment group as compared to the placebo treatment group, from baseline of –2.78% to –4.69% and p-values ranging from 0.005 to <0.001. However, weight loss was more pronounced and consistent in the cohort treated with an initial four-week, observed dosing, inpatient period, for which overall placebo subtracted weight loss from baseline at week 12 ranged from –3.87% to –4.69%, all with p-values of less than 0.005, with the most pronounced weight loss during the in-patient period. The once daily SC injection formulation also showed consistent and predictable pharmacokinetic measurements during the four-week inpatient interval in the first stage, validating the characteristics of the SC injection formulation. However, this trial demonstrated challenges in drug administration and compliance when administered in an outpatient setting in the general obese population.

Setmelanotide Phase 2 SC Injection Trial 4-week In-Patient Dosing Period: Percent Weight Loss for Setmelanotide 1.5 mg/day SC injection vs Placebo over 26 days of Observed Dosing



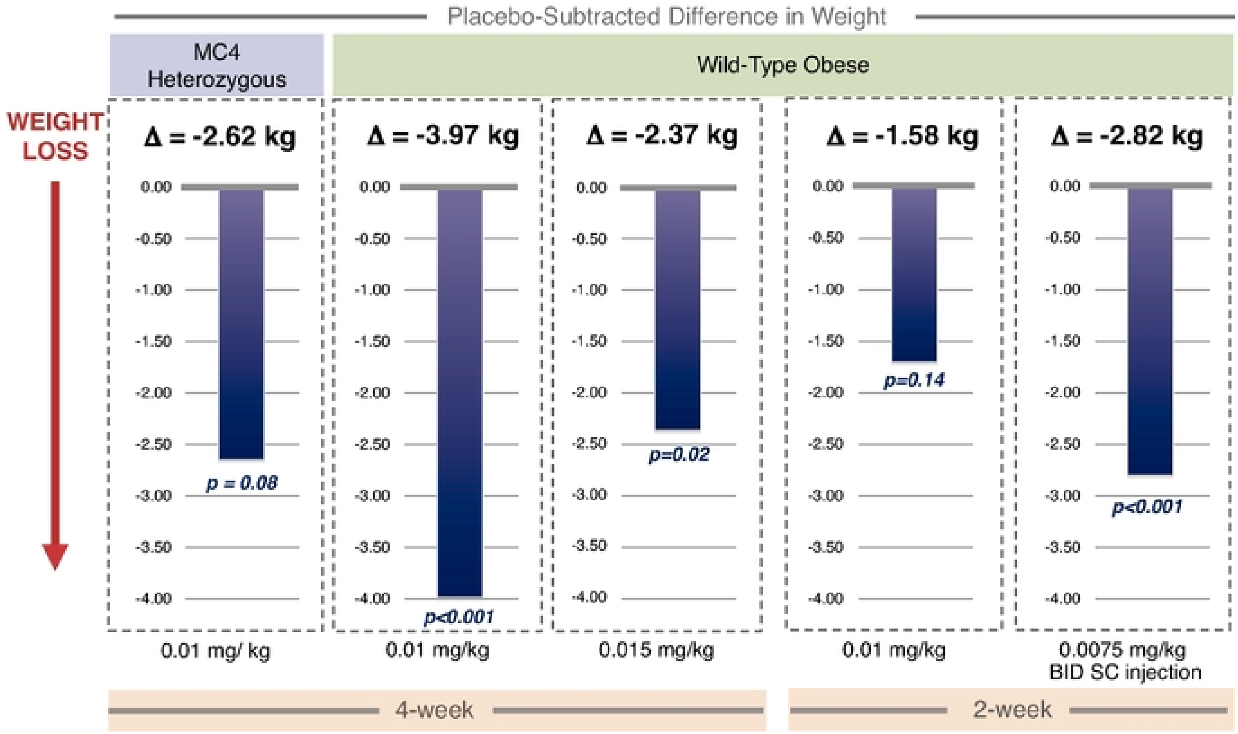
Phase 1 Clinical Development in the General Obese Population

We have completed a Phase 1 single-ascending dose, or SAD, clinical trial of setmelanotide, as well as five cohorts in a Phase 1 multiple-ascending dose, or MAD, clinical trial of setmelanotide. Both clinical trials were in healthy obese subjects, and included a double-blind, placebo-controlled randomized escalating dose design. Subjects received treatment in these Phase 1 clinical trials for one day at doses up to 0.1 mg/kg/day, which is a total daily dose of approximately 10 mg/day, and for up to 28 days at doses up to 0.015 mg/kg/day, which is a total daily dose of approximately 1.5 mg/day.

In the SAD clinical trial, our extensive monitoring of heart rate and blood pressure did not demonstrate any clinically meaningful changes with setmelanotide treatment compared with placebo. Similarly, in the MAD clinical trial, there was no evidence of any notable changes in cardiovascular parameters compared to placebo when assessed by 24-hour ambulatory blood pressure monitoring, or ABPM. We determined that the terminal half-life of setmelanotide is approximately nine to ten hours, making it suitable for once daily dosing.

Four cohorts of the Phase 1 MAD clinical trial that included doses of greater than 0.01 mg/kg/day, which is approximately 1 mg/day, for two to four weeks, demonstrated placebo subtracted weight loss differences. Most panels showed statistically significant, placebo subtracted weight reduction that ranged from 0.6 to 1.4 kg/week, with a mean of approximately 0.9 kg/week over the two to four weeks of treatment in Phase 1.

Setmelanotide: Phase 1b General Obesity Patients: Placebo Subtracted Differences(1)(2)



(1) Over two to four weeks of treatment with setmelanotide by continuous SC infusion. Placebo subtracted differences are the FDA's primary weight loss analysis approach, assessing the weight difference between active and placebo treatment groups for changes from baseline for weight.
(2) Preliminary data.

D = Placebo subtracted weight loss from baseline.

BID = Two times per day.

Phase 1 Energy Expenditure Clinical Trial

In collaboration with the National Institute of Diabetes, Digestive and Kidney Diseases, we investigated setmelanotide in a Phase 1 clinical trial to determine the effects of setmelanotide on energy expenditure, a mechanism for weight loss, in addition to the well-known effects of MC4R agonists on appetite and food intake. Twelve obese adults were randomized to receive setmelanotide or placebo by continuous SC infusion over 72 hours, followed immediately by crossover to the other treatment. Setmelanotide showed statistically significant 6.85% increases in resting energy expenditure, supporting a role for setmelanotide in weight regulation. This trial provided the first clinical demonstration that MC4R activation with setmelanotide increases resting energy expenditure in obese humans.

Long-Acting Setmelanotide Pharmacokinetic Trial

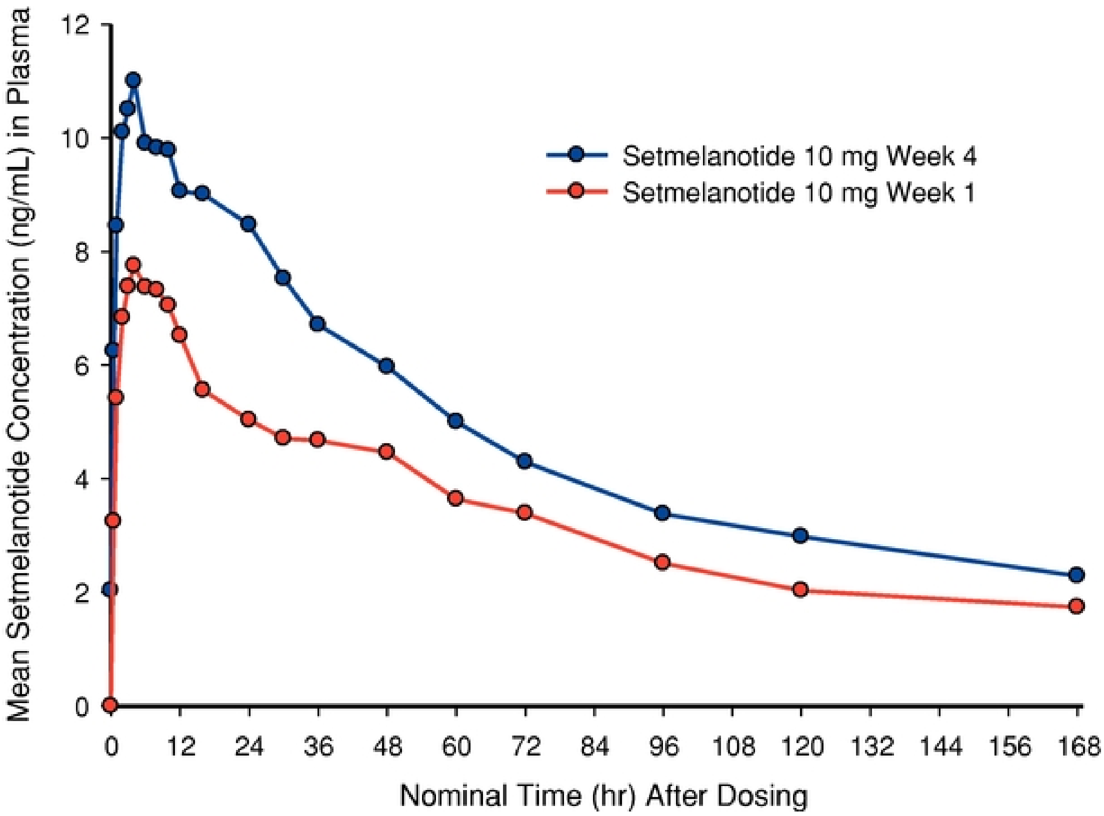
In addition to developing the once daily SC injectable formulation of setmelanotide that we are using in our ongoing clinical trials, in collaboration with Camurus AB, or Camurus, we have developed a once weekly, long-acting formulation using FluidCrystal® technology. When injected subcutaneously, aqueous body fluid is absorbed by the excipient lipid phase which forms a gel-like depot consisting of liquid crystals formed in situ leading to slow diffusion of setmelanotide from the depot.

We have compelling preclinical data with the long-acting formulation: in monkeys, the terminal half-life of the long-acting formulation is approximately 105 hours, and in rats, approximately 92 hours. Two-week toxicology studies in rats have been completed, and the long-acting formulation was well tolerated. During the two-week dosing period, animals given setmelanotide had dose-related, statistically significant lower body weights, from –9.8% to –11.7%, compared to those given placebo controls. Food consumption for animals given setmelanotide was also lower compared to controls, which decreased by approximately –20.5%.

Two parts of this clinical pharmacokinetic trial are completed, defining the single-dose and multiple-dose pharmacokinetics of this formulation. The first part, Part A, is an ascending-dose, placebo-controlled, up to three sequential panel PK trial, and PK and safety/tolerability will be collected for approximately 14 days. Dose for the three panels will range from 2.5 mg up to 30 mg given as a single SC injection. The second part, Part B, is a placebo-controlled, single panel of 12 normal healthy obese patients who received four once-weekly injections of 10 mg setmelanotide long-acting formulation.

The results from Part A demonstrate that a 10 mg single subcutaneous dose showed a profile that was consistent with once weekly dosing with a mean pharmacokinetic half-life of 123 hours. Following the completion of the single-dose part, we completed Part B, with multiple dosing in order to evaluate the extended-release, once-weekly formulation of setmelanotide. Multiple dosing of the formulation demonstrated tolerability and pharmacokinetics that support further clinical development. While this data is preliminary, and this formulation is anticipated to be only ready for submission in 2021, or later, this simpler dosing regimen may provide improvements in patient convenience, and may provide additional advantages in the pediatric population.

Mean setmelanotide concentrations (ng/mL) in plasma during weeks 1 and 4 following 10 mg subcutaneous weekly injections of a Camurus formulation



Safety and Tolerability

Historically, clinical data with other MC4R therapies suggested that MC4R-mediated side effects may include changes in blood pressure and heart rate, increased erections in males, changes in libido and sexual function in females and nausea and vomiting. As a result, primarily due to concerns about blood pressure and heart rate changes, none of these therapies have proceeded to commercialization and no other MC4R agonists are currently in the clinic for the treatment of obesity and/or hyperphagia. It is noteworthy that the pattern of effects differed among each of the other MC4R therapies, underscoring the complex physiology of MC4R. With setmelanotide, there has been little, if any, evidence of blood pressure or heart rate changes, preliminarily supporting an important differentiation of setmelanotide from previous MC4R therapies. Careful monitoring for blood pressure and heart rate changes, as well as other potential adverse events, is included in all setmelanotide clinical trials.

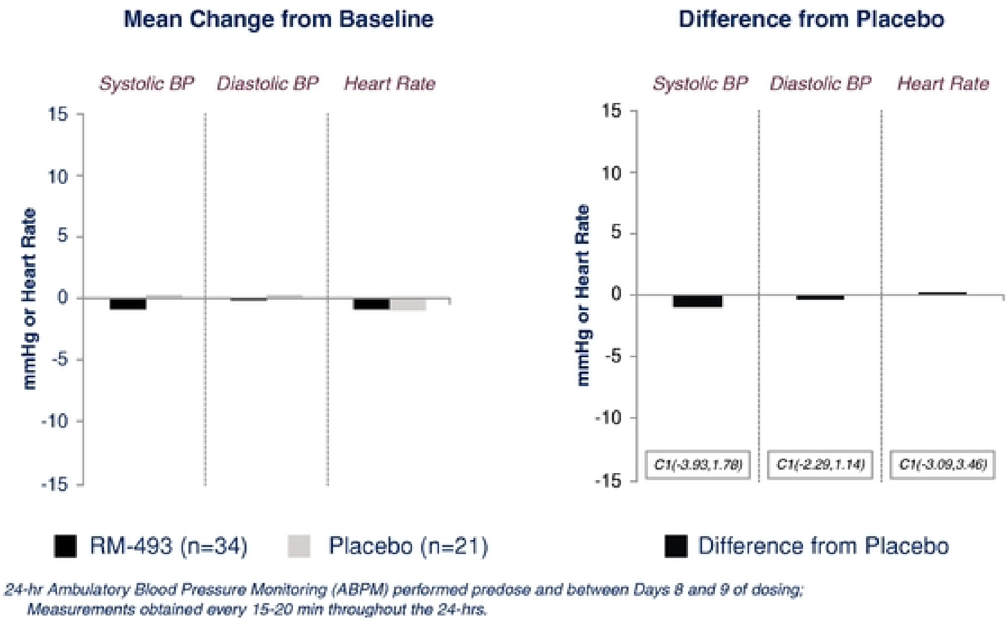
Because of these first generation MC4 therapy failures, the setmelanotide program employed an intensive preclinical screening program to assess clinical candidates for blood pressure and heart rate effects, along with efficacy. The cornerstone of this preclinical screening program was a significant investment in obese primate studies which validated setmelanotide as a promising compound for clinical development. More recently, new research supporting a unique mechanism of action of setmelanotide, compared to earlier MC4R agonists and the endogenous ligand MSH, was published in May 2018 in Nature Medicine.

Setmelanotide was generally well tolerated in our Phase 1 and Phase 2 clinical trials, and in very preliminary data from our ongoing Phase 3 trials. Overall, except as outlined below, the number and patterns of adverse events was generally low, and the intensity of the adverse events was generally mild, and infrequently led to clinical trial discontinuation.

There has been only a single serious adverse event possibly attributed to setmelanotide in our clinical trials. In our Phase 2 clinical trial with once daily SC injection, one patient was hospitalized for unusual chest pain, but no evidence of any serious respiratory or cardiac cause was found after careful evaluation, and the event was attributed to musculoskeletal pain. There were no treatment-related changes in physical examination, except as noted below, and few, if any, clinically relevant changes in electrocardiograms, laboratory data and/or anti-drug antibodies. Overall, there have been ten other serious adverse events in the full development program, in addition to the serious adverse event described above: seven others on setmelanotide, mostly from open label trials, including left arm numbness, influenza immunization reaction, pancreatitis secondary to pre-existing gallstones, pneumonia, hypoglycemia due to acute adrenal insufficiency, due to non-compliance with hydrocortisone regimen, a depressive episode with elective admission to a psychiatry ward in a patient with history of depression and who continued on treatment, and rotavirus-related gastroenteritis. There were also three serious adverse events during treatment with placebo, consisting of biliary dyskinesia, severe groin strain, and pelvic inflammatory disease. None of these serious adverse events was considered related to setmelanotide treatment.

To demonstrate that setmelanotide has the potential to provide a safe cardiovascular profile, we extensively validated setmelanotide in obese primate preclinical studies, with special attention to cardiovascular effects. The results of these studies supported testing in clinical trials. In the clinical trials, we monitored blood pressure and heart rate extensively, primarily by 24-hour ABPM. In most clinical trials, there were multiple 24-hour ABPM periods, both on a pre-treatment and post-treatment basis. Trial-by-trial review of the 24-hour ABPM data shows little, if any, evidence of changes in heart rate and/or blood pressure even at the highest doses tested in Phase 1 and Phase 2 clinical trials. We have also conducted an analysis of 24-hour ABPMs that were obtained pre-dose and post-dose across completed studies, which was presented at the Obesity Society in 2015. This included 128 patients, of which 79 were active and 49 were on a placebo. Overall, there was little, if any, evidence of blood pressure or heart rate changes evident from baseline versus placebo in any trial, preliminarily supporting an important differentiation of setmelanotide from previous MC4 therapies. While the preliminary data are encouraging, there will be continued focus on potential cardiovascular risk until addressed in larger and longer clinical trials.

Setmelanotide Phase 2 SC Injection Trial: 24-hr ABPM (All Studied Patients), Showing No Adverse Effect of Setmelanotide on Blood Pressure or Heart Rate



In the majority of our trials, there was a small increase in penile erections in male patients, as well as signs of sexual arousal in a small number of female patients. These symptoms were infrequent, generally mild, not painful, and short-lived. Most often these symptoms were reported in the first week of treatment. There was a small incidence of nausea and vomiting, as well as injection site reactions, both of which usually were reported as mild, early in treatment, and short-lived. A small number of patients had dose reductions and/or discontinued treatment due to nausea and vomiting.

We also noted darkening of skin and skin lesions, such as moles and freckles, in most patients who received setmelanotide. This was likely caused by activation of the closely related MC1 receptor, the receptor that mediates skin darkening in response to sun exposure. This was observed generally after one to two weeks of treatment, most often plateaued by two to four weeks of treatment, and like sun-related tanning, generally returned to baseline after cessation of exposure.

Additional adverse events noted at somewhat greater rates numerically for setmelanotide compared to placebo across the clinical program include fatigue and related symptoms, diarrhea, arthralgia, back pain and headache, but most investigators reported these effects to be unrelated to setmelanotide.

While general obese patients are not currently the focus of setmelanotide studies, the FDA and EMA consider the risk and benefit information observed to date with setmelanotide in general obese patients to be supportive of the continued development of this therapy. These data from general obese patients do not raise any new safety concerns and suggest that substantial benefit, as evidenced by weight loss, is possible.

Preclinical Development

Preclinical studies demonstrated the efficacy of setmelanotide in suppressing food intake and body weight gain in diet-induced obese mice, rats, dogs, and rhesus macaques, as well as in genetic models of obesity, including leptin-deficient ob/ob mice and obese Zucker, or fa/fa (leptin-receptor deficient), rats. Furthermore, setmelanotide is associated with restoring insulin sensitivity in nonclinical models of obesity in rodents and lowering of plasma triglycerides, cholesterol, and free fatty acids.

In particular, we demonstrated activity in obese non-human primates, where approximately 13% weight loss was demonstrated with eight weeks of treatment, without evidence of cardiovascular toxicity. We also studied obese primates in crossover studies to confirm the lack of cardiovascular toxicity by setmelanotide in obese primates. These preclinical studies also confirmed the cardiovascular effects of previous MC4 therapies that had produced cardiovascular toxicity in humans. In contrast, setmelanotide was without cardiovascular effects in head-to-head studies.

Lastly, the toxicology program to support the NDA filing of setmelanotide for POMC deficiency obesity is completed. We completed three-month toxicology studies in rats and monkeys, with doses and exposures that are more than 300-fold greater than those at the anticipated clinical doses without evidence of clinically relevant toxicological findings. Similarly, we have also completed chronic toxicity studies (6-month rat, 9-month monkey), which in rats provided 219- (maximum concentration) and 106-times (area under the curve), respectively, and in monkeys 282- and 82-times, respectively, the exposures at the anticipated clinical doses compared to the No-Observed-Adverse-Effect-Level(s) in animals. We have evaluated the potential reproductive and development effects of setmelanotide in rats and rabbits with administration by SC injection, to support the administration of setmelanotide in women of child-bearing potential. In addition, a juvenile toxicology study has been completed that will support dosing in pediatric patients less than 12 years of age. In addition, we are planning carcinogenicity studies, the longest of which is expected to be two years. The FDA has allowed us to defer carcinogenicity studies until after approval of an NDA for setmelanotide. We believe this also to be true for the EMA, however, the EMA has not yet provided firm guidance on the need for one or more carcinogenicity studies at time of filing.

RM-853, a Preclinical Ghrelin O-Acyltransferase Inhibitor

In addition to our development of setmelanotide, in April 2018, we announced that we had acquired exclusive, worldwide rights from Takeda Pharmaceutical Company Limited, or Takeda, to develop and commercialize RM-853. RM-853 is a potent, orally available GOAT inhibitor currently in preclinical development for PWS. PWS is a rare genetic disorder that results in hyperphagia and early-onset, life-threatening obesity, for which there are no approved therapeutic options. RM-853 is currently in pre-clinical development. We anticipate filing an IND for RM-853 with the FDA in 2020.

Ghrelin is an orexigenic peptide, secreted by the stomach and proximal small intestine in response to a negative energy balance. Ghrelin can play a key physiological role in stimulating appetite and promoting food intake, thereby maintaining overall energy balance. In people living with PWS, levels of active ghrelin are elevated, contributing to hyperphagia, which leads to severe obesity. RM-853 is designed to block GOAT, the key enzyme involved in the production of the active form of ghrelin, with the expected effect of lowering active ghrelin levels. This blockage also increases the levels of des-acyl-ghrelin, or DAG, a ghrelin precursor; high levels of DAG are believed to have independent beneficial effects on the control of appetite and tissue homeostasis, which might add to the potential efficacy of RM-853 in PWS. In preclinical research, RM-853 prevented body weight gain and reduced fat mass in high fat-fed mice, with a favorable pharmacokinetic, pharmacodynamic, and safety profile. We plan to complete preclinical studies of RM-853 and file an IND with the FDA in approximately the first quarter of 2020. Under the terms of the agreement, we will assume sole responsibility for the global product development and commercialization of RM-853.

Competition

The biotechnology and pharmaceutical industries are intensely competitive and subject to rapid and significant technological change. We have competitors in a number of jurisdictions, many of which have substantially greater name recognition, commercial infrastructures and financial, technical and personnel resources than we have. Established competitors may invest heavily to quickly discover and develop compounds that could make setmelanotide obsolete or uneconomical. Any new product that competes with an approved product may need to demonstrate compelling advantages in efficacy, convenience, tolerability and safety to be commercially successful. Other competitive factors, including generic competition, could force us to lower prices or could result in reduced sales. In addition, new products developed by others could emerge as competitors to setmelanotide. If we are not able to compete effectively against our current and future competitors, our business will not grow and our financial condition and operations will suffer.

There are no current pharmacological treatments for regulating hunger and hyperphagia-related behaviors of patients with PWS. In contrast with the absence of companies who have disclosed efforts to study upstream disorders of the MC4 pathway, we are aware of several companies investigating or developing therapies intended to treat hunger and hyperphagia associated with PWS. The different companies and compounds in development, of which we are aware, involve multiple mechanisms of action. The companies and their compounds include; Millendo Therapeutics Inc. (AZP-531), Soleno Therapeutics (Diazoxide Choline Controlled Release), Zafgen (ZGN-1258), GLWL Research Inc. (GLWL-01), Insys Therapeutics Inc. (Oral Cannabidiol Solution) and Calm Therapeutics.

Licensing Agreements

Ipsen Pharma S.A.S.

In February 2010, the Predecessor Company entered into a license agreement with Ipsen S.A.S., or Ipsen, pursuant to which Ipsen granted to it an exclusive, sublicensable, worldwide license to certain patents and other intellectual property rights to research, develop, and commercialize compounds that were discovered or researched by Ipsen in the course of conducting its MC4 program or that otherwise were covered by the licensed patents. Rights under the license included the right to research, develop and commercialize setmelanotide. Pursuant to the license, Ipsen also granted to the Predecessor Company a non-exclusive, sublicensable, worldwide license to certain patents and other intellectual property rights that were licensed by Ipsen from a third party or that Ipsen may develop in the future to research, develop, and commercialize any of the compounds exclusively licensed by Ipsen pursuant to the license. See "*Management's Discussion and Analysis of Financial Condition and Results of Operations—Corporate Background and Distribution*."

On March 21, 2013, the LLC entity completed the Corporate Reorganization pursuant to which, among other things, the existing license with Ipsen with respect to the MC4 program is now held separately by us. As a result, we hold the rights to the MC4 program, including the rights to develop and commercialize setmelanotide. See "*Management's Discussion and Analysis of Financial Condition and Results of Operations—Corporate Background and Distribution*."

Under the terms of the Ipsen license agreement, Ipsen will receive payments of up to $40.0 million upon the achievement of certain development and commercial milestones in connection with the development, regulatory approval and commercialization of applicable licensed products, and royalties on future sales of the licensed products. Substantially all of the aggregate payments under the Ipsen license agreement are for milestones that may be achieved no earlier than first commercial sale of the applicable licensed product. Royalties in the mid-single digits on future sales of the applicable licensed products will be due under the Ipsen license agreement on a licensed product-by-licensed product and country-by-country basis until the later of the date when sales of a licensed product in a particular country are no longer covered by patent rights licensed pursuant to the Ipsen license agreement and the tenth anniversary of the date of the first commercial sale of the applicable licensed product in the applicable country. The term of the Ipsen license agreement continues until the expiration of the applicable royalty term on a country-by-country and product-by-product basis. Upon expiration of the term of the agreement, the licensed rights granted to us under the agreement, to the extent they remain in effect at the time of expiration, will thereafter become irrevocable, perpetual and fully paid-up licenses that survive the expiration of the term. We have a right to terminate the license agreement at any time during the term for any reason on 180 days' written notice to Ipsen. Ipsen has a right to terminate the agreement prior to expiration of its term for our material breach of the agreement, our failure to initiate or complete development of a licensed product or our bringing an action seeking to have an Ipsen license patent right declared invalid. Upon any early termination of the license agreement not due to Ipsen's material breach, all licensed rights granted under the license agreement will terminate.

Camurus

In January 2016, we entered into a license agreement for the use of Camurus' drug delivery technology, FluidCrystal, to formulate setmelanotide with Camurus. Under the terms of the agreement, Camurus granted us a worldwide license to the FluidCrystal technology to formulate setmelanotide and to develop, manufacture, and commercialize this new formulation for once-weekly dosing, administered as a SC injection. The license granted to us is specific to the FluidCrystal technology incorporating setmelanotide. Under the terms of the license agreement, we are responsible for manufacturing, development, and commercialization of the setmelanotide FluidCrystal formulation worldwide. Camurus received a non-refundable and non-creditable upfront payment of $0.5 million in January 2016, and is eligible to receive progressive payments of approximately $65.0 million, of which the majority are sales milestones. In addition, Camurus is eligible to receive tiered, mid to mid-high, single digit royalties on future sales of the product.

The term of the agreement continues until the expiration of the applicable royalty term on a country-by-country and product-by-product basis. Upon expiration of the term of the agreement, the licensed rights granted to us under the agreement, to the extent they remain in effect at the time of expiration, will thereafter become irrevocable, perpetual and fully paid-up licenses that survive the expiration of the term. We have a right to terminate the license agreement at any time during the term for any reason upon 90 days' written notice to Camurus. Camurus has a right to terminate the agreement prior to expiration of its term for our material breach of the agreement, if we voluntarily or involuntarily file for bankruptcy, or for our bringing an action seeking to have a Camurus license patent right declared invalid.

Upon any early termination of the license agreement not due to Camurus' material breach, all licensed rights granted under the license agreement will terminate.

Takeda

In March 2018, we acquired exclusive, worldwide rights from Takeda to develop and commercialize RM-853. RM-853 is a potent, orally available GOAT inhibitor currently in preclinical development for PWS. PWS is a rare genetic disorder that results in hyperphagia and early-onset, life-threatening obesity, for which there are no approved therapeutic options. We will assume sole responsibility for the global product development and commercialization of RM-853. Takeda received an upfront fee of $4.4 million which we settled in April 2018 with shares of our common stock, and is eligible to receive milestone payments of approximately $140.0 million, most of which are payable upon regulatory approval or are sales milestones. In addition, Takeda is eligible to receive back-end development milestones, and single-digit royalties on future RM-853 sales.

Among other obligations under our agreement with Takeda, Takeda has a right of first negotiation under certain circumstances to sublicense the assets we acquired from Takeda in the territory of Japan. This right of first negotiation remains in effect until the earlier of five years from the date of the agreement, consummation of a change in control, or sublicense to a third party. This may delay or limit our ability to enter into certain transactions with respect to this product candidate.

The term of the agreement continues until the expiration of the applicable royalty term on a country-by-country and product-by-product basis. Upon expiration of the term of the agreement, the licensed rights granted to us under the agreement, to the extent they remain in effect at the time of expiration, will thereafter become irrevocable, perpetual and fully paid-up licenses that survive the expiration of the term. We have a right to terminate the license agreement at any time during the term for any reason upon 90 days' written notice to Takeda. Takeda has a right to terminate the agreement prior to expiration of its term for our material breach of the agreement, if we voluntarily or involuntarily file for bankruptcy, or for our bringing an action seeking to have a Takeda license patent right declared invalid. Upon any early termination of the license agreement not due to Takeda's material breach, all licensed rights granted under the license agreement will terminate.

Commercial Operations

Our commercial strategies center around creating a well-informed, supportive genetic obesity community of institutions, healthcare providers, patients, caregivers, and payers to support our ongoing research and development efforts to transform the care of patients with MC4 pathway deficiencies.

Our commercial priorities for the launch of setmelanotide include:

- Improving methods of evaluation and diagnosis of rare genetic obesity patients through enhanced diagnostic capabilities and partnership with key opinion leaders and pediatric endocrinologists in order to more clearly articulate the clinical presentation of these patients to referring physicians;
- Facilitating an integrated genetic obesity community through services that support patient awareness, education, advocacy, and treatment;
- Communicating the burden of rare genetic obesity syndromes to promote advocacy for patient sequencing and support for pricing and reimbursement of setmelanotide; and
- Building a global commercial organization to drive patient identification and enable a successful launch of setmelanotide.

Our management team understands the complexity of rare diseases and we believe has the necessary expertise to be a true partner to patients, caregivers, advocacy, and healthcare teams leading to shared success. We intend to establish a specialty sales force and develop an organizational infrastructure that will support an extensive network of endocrinologists and other physicians treating severe childhood obesity and rare genetic disorders of obesity which in turn we believe will help establish genetic obesity centers of excellence. Our goal is for our field personnel to work directly with patients, caregivers and healthcare providers to facilitate therapy initiation and adherence. We also expect to partner with existing and new advocacy organizations to further educate our patient population on genetic obesity and support coverage for setmelanotide. In addition, we intend to establish our own commercial sales and marketing organization in the United States and core strategic markets and to selectively establish partnerships in markets outside the United States for sales, marketing, and distribution.

Patents and Proprietary Rights

We have in-licensed a large patent portfolio from Ipsen for our melanocortin programs. The portfolio includes multiple patent families, and all of these in-licensed patent families are being prosecuted or maintained by Ipsen in consultation with us. We have also filed patent applications in five families which are exclusively owned and maintained by us that relate to the melanocortin program.

Our MC4 portfolio of licensed and exclusively owned patent families, which includes setmelanotide, consists of 12 patent families currently being prosecuted or maintained, which include applications and patents directed to compositions of matter, formulations and methods of treatment using setmelanotide. As of June 8, 2018, the portfolio for the MC-4 program consists of 14 issued United States patents and 54 issued non-United States patents across eight of the 12 families. We are actively pursuing eight United States patent applications and 43 non-United States applications in 12 jurisdictions.

In the patent family directed to selected MC4 receptor agonists, including the composition of matter for setmelanotide, we have three issued United States patents and 26 issued non-United States patents, including Australia, Canada, China, Europe, Hong Kong, India, Israel, Japan, Korea, New Zealand, Russia and Singapore. The standard 20-year term for patents in this family would expire in 2026, but two of the United States patents are expected to expire in 2027 due to patent term adjustments. Patent term extensions for delays in marketing approval may also extend the terms of patents in this family.

In addition to the patents and patent applications discussed above, we co-own one patent family with Charité-Universitätsmedizin Berlin, which has been filed in 21 jurisdictions. We have also filed one application in the United States co-owned with the University of Strasbourg and the French National Institute of Health and Medical Research. These applications relate to the melanocortin program and, have not yet entered active prosecution.

We have also in-licensed a patent family from Takeda directed to the composition of matter and methods of use of ghrelin O-acetyltransferase inhibitors, including RM-853. This patent family includes one issued United States patent, nine issued non-United States patents including China, Europe, and Japan, and one pending application in Canada. The standard 20-year term for the patents in this family will expire in 2033, though patent term extensions for delays in marketing approval may also extend the terms of patents in this family.

Intellectual Property Protection Strategy

We currently seek, and intend to continue seeking, patent protection whenever commercially reasonable for any patentable aspects of setmelanotide and related technology or any new products or product candidates we acquire in the future. Where our intellectual property is not protected by patents, we may seek to protect it through other means, including maintenance of trade secrets and careful protection of our proprietary information. Our license from Ipsen for the melanocortin program require Ipsen, subject to certain exceptions and upon consultation with us, to prosecute and maintain its patent rights as they relate to the licensed compounds and methods. If Ipsen decides to cease prosecution or maintenance of any of the licensed patent rights, we have the option to take over prosecution and maintenance of those patents and Ipsen will assign to us all of its rights in such patents. For those patent rights that we own exclusively, we control all prosecution and maintenance activities.

The patent positions of biopharmaceutical companies are generally uncertain and involve complex legal, scientific and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Consequently, we do not know whether the product candidate we in-license will be protectable or remain protected by enforceable patents. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction, and furthermore, we cannot determine whether the claims of any issued patents will provide sufficient proprietary protection to protect us from competitors, or will be challenged, circumvented or invalidated by third parties. Because patent applications in the United States and certain other jurisdictions are maintained in secrecy for 18 months, and since publication of discoveries in the scientific or patent literature often lags behind actual discoveries, we cannot be certain of the priority of inventions covered by pending patent applications. This potential issue is exacerbated by the fact that, prior to March 16, 2013, in the United States, the first to make the claimed invention may be entitled to the patent. On March 16, 2013, the United States transitioned to a "first to file" system in which the first inventor to file a patent application may be entitled to the patent. Therefore, we may have to participate in interference proceedings declared by the United States Patent and Trademark Office, or PTO, or a foreign patent office to determine priority of invention. Moreover, we may have to participate in other proceedings declared by the United States PTO or a foreign patent office, such as post-grant proceedings and oppositions, that challenge the validity of a granted patent. Such proceedings could result in substantial cost, even if the eventual outcome is favorable to us.

Although we currently have issued patents directed to a number of different attributes of our products, and pending applications on others, there can be no assurance that any issued patents would be held valid by a court of competent jurisdiction. An adverse outcome could subject us to significant liabilities to third parties, require disputed rights to be licensed from third parties or require us to cease using specific compounds or technology. To the extent prudent, we intend to bring litigation against third parties that we believe are infringing our patents.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the earliest date of filing a non-provisional patent application. In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the United States PTO in granting a patent, or may be shortened if a patent is terminally disclaimed over another patent with an earlier expiration date.

As mentioned above, in the United States, the patent term of a patent that covers an FDA-approved drug may also be eligible for patent term extension, which permits patent term restoration as compensation for the patent term lost during the FDA regulatory review process. In the future, if and when our pharmaceutical products receive FDA approval, we expect to apply for patent term extensions on patents covering those products. We intend to seek patent term adjustments and extensions to any of our issued patents in any jurisdiction where these are available, however there is no guarantee that the applicable authorities, including the FDA in the United States, will agree with our assessment of whether such extensions should be granted, and even if granted, the length of such adjustments or extensions.

To protect our rights to any of our issued patents and proprietary information, we may need to litigate against infringing third parties, or avail ourselves of the courts or participate in hearings to determine the scope and validity of those patents or other proprietary rights. These types of proceedings are often costly and could be very time-consuming to us, and we cannot be certain that the deciding authorities will rule in our favor. An unfavorable decision could result in the invalidation or a limitation in the scope of our patents or forfeiture of the rights associated with our patents or pending patent applications. Any such decision could result in our key technologies not being protectable, allowing third parties to use our technology without being required to pay us licensing fees or may compel us to license needed technologies from third parties to avoid infringing third-party patent and proprietary rights. Such a decision could even result in the invalidation or a limitation in the scope of our patents or could cause us to lose our rights under existing issued patents or not to have rights granted under our pending patent applications.

In addition, we intend to seek orphan drug exclusivity in jurisdictions in which it is available. A prerequisite to orphan drug exclusivity in the United States and in the European Union is orphan drug designation. An orphan drug designation may be granted where a drug is developed specifically to treat a rare or uncommon medical treatment. If a product which has an orphan drug designation subsequently receives the first regulatory approval for the indication for which it has such designation, the product is entitled to orphan exclusivity, meaning that the applicable regulatory authority may not approve any other applications to market the same drug for the same indication, except in certain very limited circumstances, for a period of seven years in the United States and 10 years in the European Union. Orphan drug exclusivity does not prevent competitors from developing or marketing different drugs for an indication.

We also rely on trade secret protection for our confidential and proprietary information. Although we take steps to protect our proprietary information and trade secrets, including through contractual means with our employees and consultants, no assurance can be given that others will not independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets or disclose such technology, or that we can meaningfully protect our trade secrets. It is our policy to require our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors to execute confidentiality agreements upon the commencement of employment or consulting relationships with us. These agreements provide that all confidential information developed or made known to the individual during the course of the individual's relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances. In the case of employees, the agreements provide that all inventions conceived by the individual will be our exclusive property. There can be no assurance, however, that these agreements will provide meaningful protection or adequate remedies for our trade secrets in the event of unauthorized use or disclosure of such information.

Manufacturing

We currently contract with a third party for the manufacture of setmelanotide and intend to continue to do so in the future. We have entered into a process development and manufacturing services agreement with CordenPharma International, formerly Peptisyntha SA prior to its acquisition by CordenPharma International, or Peptisyntha, under which Peptisyntha will provide certain process development and manufacturing services in connection with the manufacture of setmelanotide. Under the agreement, we pay Peptisyntha for services in accordance with the terms of mutually agreed upon work orders, which we and Peptisyntha may enter into from time to time. The agreement also provides that, subject to certain conditions, for a period following each product launch date, we will source from Peptisyntha a portion of our requirements for that product being sourced from non-affiliate third parties. Under the agreement, each party is subject to customary indemnification provisions.

The Peptisyntha agreement will continue, unless earlier terminated pursuant to its terms, until the later of six years from the July 17, 2013 effective date or the completion of all services under all work plans executed in accordance with the terms of the agreement prior to the sixth anniversary of its effective date. The agreement may be extended by us continuously for additional two-year periods upon written notice to Peptisyntha. We also may terminate the agreement or any work order thereunder upon at least 30 days' prior written notice to Peptisyntha.

We have also entered into a process development and manufacturing services agreement with Recipharm Monts S.A.S., or Recipharm, under which Recipharm will provide certain process development and manufacturing services in connection with the manufacture of setmelanotide. Under the agreement, we pay Recipharm for services in accordance with the terms of mutually agreed upon work orders, which we and Recipharm may enter into from time to time. Under the agreement, each party is subject to customary indemnification provisions. The Recipharm agreement will continue, unless earlier terminated pursuant to its terms, until the later of three years from the December 21, 2016 effective date or the completion of all services under all work plans executed in accordance with the terms of the agreement prior to the third anniversary of its effective date. The agreement may be extended by us continuously for additional two-year periods upon written notice to Recipharm. We also may terminate the agreement or any work order thereunder upon at least 60 days' prior written notice to Recipharm.

Our contract manufacturing agreements give us visibility into the expected future cost of producing setmelanotide at commercial scale. Based upon a range of prices of currently-marketed therapies indicated for orphan diseases, we believe that our cost of goods for setmelanotide will be highly competitive.

We currently have no plans to build our own clinical or commercial scale manufacturing capabilities. To meet our projected needs for clinical supplies to support our activities through regulatory approval and commercial manufacturing, the contract manufacturing organizations, or CMOs, with whom we currently work will need to increase scale of production or we expect that we will need to secure alternate suppliers. We have not currently identified alternate suppliers in the event the current CMOs we utilize are unable to scale production. Because we rely on these CMOs, we have personnel with pharmaceutical development and manufacturing experience who are responsible for maintaining our CMO relationships.

Regulatory Matters

Government Regulation and Product Approvals

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the European Union, extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of pharmaceutical products. The processes for obtaining marketing approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other competent authorities, require the expenditure of substantial time and financial resources.

Review and Approval of Drugs in the United States

In the United States, the FDA approves drug products under the Federal Food, Drug, and Cosmetic Act, or FDCA, and associated implementing regulations. Biological products, on the other hand, are licensed by the FDA under the Public Health Service Act, or PHSA. With passage of the Biologics Price Competition and Innovation Act of 2009, Congress amended the definition of "biological product" in the PHSA so as to exclude a chemically synthesized polypeptide from licensure under the PHSA. Rather, the Act provided that such products would be treated as drugs under the FDCA. Subsequently, through final guidance issued in April 2015, the FDA indicated that a "chemically synthesized polypeptide" is any alpha amino acid polymer that is made entirely by chemical synthesis and is less than 100 amino acids in size. Accordingly, based on this FDA guidance, we believe that our products will not be treated as biologics subject to approval of a biologics license application, or BLA, by the FDA, and rather will be treated as drug products subject to approval of a new drug application, or NDA, by the FDA pursuant to the FDCA.

The failure to comply with applicable requirements under the FDCA and other applicable laws at any time during the product development process, approval process or after approval may subject an applicant and/or sponsor to a variety of administrative or judicial sanctions, including refusal by the FDA to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and other types of letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, or civil or criminal investigations and penalties brought by the FDA and the Department of Justice or other governmental entities.

An applicant seeking approval to market and distribute a new drug product in the United States must typically undertake the following:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or GLP, regulations;
- submission to the FDA of an IND, which must take effect before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with current Good Clinical Practices, or cGCPs, to establish the safety and efficacy of the proposed drug product for each proposed indication;
- preparation and submission to the FDA of an NDA requesting marketing for one or more proposed indications;
- review by an FDA advisory committee, where appropriate or if applicable, as may be requested by the FDA to assist with its review;
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the product, or components thereof, are produced to assess compliance with current Good Manufacturing Practices, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;
- satisfactory completion of FDA audits of clinical trial sites to assure compliance with cGCPs and the integrity of the clinical data;
- payment of user fees, per published Prescription Drug User Fee Act, or PDUFA, guidelines for the relevant year, and securing FDA approval of the NDA; and
- compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, and the potential requirement to conduct post-approval studies.

Preclinical Studies

Before an applicant begins testing a compound with potential therapeutic value in humans, the drug candidate enters the preclinical testing stage. Preclinical studies include laboratory evaluation of product chemistry, toxicity and formulation, as well as *in vitro* and animal studies to assess the potential safety and activity of the drug for initial testing in humans and to establish a rationale for therapeutic use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations. The results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, are submitted to the FDA as part of an IND. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, may continue after the IND is submitted.

The IND and IRB Processes

An IND is an exemption from the FDCA that allows an unapproved drug to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer an investigational drug to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug that is not the subject of an approved NDA. In support of a request for an IND, applicants must submit a protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, are submitted to the FDA as part of an IND. The FDA requires a 30-day waiting period after the filing of each IND before clinical trials may begin. This waiting period is designed to allow the FDA to review the IND to determine whether human research subjects will be exposed to unreasonable health risks. At any time during this 30-day period, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold. In this case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin.

Following commencement of a clinical trial under an IND, the FDA may also place a clinical hold or partial clinical hold on that trial. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. For example, a specific protocol or part of a protocol is not allowed to proceed, while other protocols may do so. No more than 30 days after imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following issuance of a clinical hold or partial clinical hold, an investigation may only resume after the FDA has notified the sponsor that the investigation may proceed. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or otherwise satisfying the FDA that the investigation can proceed.

A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND. When a foreign clinical study is conducted under an IND, all FDA IND requirements must be met unless waived. When the foreign clinical study is not conducted under an IND, the sponsor must ensure that the study complies with certain regulatory requirements in order to use the study as support for an IND or application for marketing approval. Specifically, on April 28, 2008, the FDA amended its regulations governing the acceptance of foreign clinical studies not conducted under an IND or a NDA. The final rule provides that such studies must be conducted in accordance with good clinical practice, or GCP, including review and approval by an independent ethics committee, or IEC, and informed consent from subjects. The GCP requirements in the final rule encompass both ethical and data integrity standards for clinical studies. The FDA's regulations are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical studies, as well as the quality and integrity of the resulting data. They further help ensure that non-IND foreign studies are conducted in a manner comparable to that required for IND studies.

In addition to the foregoing IND requirements, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review and reapprove the study at least annually. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations. An IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the product candidate has been associated with unexpected serious harm to patients.

Additionally, some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a trial may move forward at designated check points based on access that only the group maintains to available data from the study. Suspension or termination of development during any phase of clinical trials can occur if it is determined that the participants or patients are being exposed to an unacceptable health risk. Other reasons for suspension or termination may be made by us based on evolving business objectives and/or competitive climate.

Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on its ClinicalTrials.gov website.

Human Clinical Studies in Support of an NDA

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the inclusion and exclusion criteria, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated.

Human clinical trials are typically conducted in the following sequential phases, which may overlap or be combined:

- Phase 1: The drug is initially introduced into healthy human subjects or, in certain indications such as cancer, patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness and to determine optimal dosage.

- Phase 2: The drug is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.

- Phase 3: The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product, and to provide adequate information for the labeling of the product.

- Phase 4: Post-approval studies, when applicable, are conducted following initial approval, typically to gain additional experience and data from treatment of patients in the intended therapeutic indication.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the drug; and any clinically important increase in the case of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

During the course of clinical development, the sponsor often refines the indication and endpoints on which the NDA will be based. For endpoints based on PROs and OROs, the process typically is an iterative one. The FDA has issued guidance on the framework it uses to evaluate PRO instruments, and it may offer advice on optimizing PRO and ORO instruments during the clinical development process, but the FDA usually reserves final judgment until it reviews the NDA.

Concurrent with clinical trials, companies often complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, must develop methods for testing the identity, strength, quality, purity and potency of the final drug. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

In a general guidance meeting with FDA review staff in 2013, following the opening of our independent new drug application for the development of setmelanotide, the FDA provided us with general principles to follow in designing clinical studies for drugs intended for use in an indication targeted to a specific obese population. In 2015, we received further guidance from FDA review staff in a meeting to discuss clinical endpoints and trial design strategies for the study of setmelanotide in patients with rare genetic forms of obesity. At that meeting, the FDA noted its experience in applying regulatory flexibility for drugs intended to treat rare diseases. It indicated that it would take into account factors related to particular patient populations, such as the prevalence and severity of the disease, but also noted that the requirements for a phase 3 program would depend on the effect observed and the robustness of the results. The FDA also indicated that it would exercise flexibility regarding the timing and requirements for certain preclinical toxicology testing. Additional meetings occurred in 2017 and 2018. We intend to continue to take advantage of our Breakthrough Therapy designation by continuing to meet regularly with FDA review staff to discuss methods to shorten the development timeline for indication in POMC deficiency obesity, LEPR deficiency obesity, Bardet-Biedl syndrome, and Alström syndrome, and to use the knowledge gained to do likewise for other closely-related indications in rare genetic forms of obesity.

Submission and Review of an NDA by the FDA

Assuming successful completion of required clinical testing and other requirements, the results of the preclinical studies and clinical trials, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the drug product for one or more indications. Under the Prescription Drug User Fee Amendments of 2017 (PDUFA VI), the submission of most NDAs is additionally subject to a human drug application fee, which is collected at the time of submission. PDUFA VI eliminated user fees for supplements and establishments. In addition, the sponsor of an approved NDA is also subject to annual program fee rather than product fees under the previous iteration of PDUFA. For federal fiscal year 2018, the submission of an NDA for which clinical data (other than bioavailability or bioequivalence studies) with respect to safety or effectiveness are required for approval is subject to an application user fee of $2,421,495. The annual program user fee for fiscal year 2018 is $304,162.

Certain exceptions and waivers are available for some of these fees, such as an exception from the application fee for drugs with orphan designation and a waiver for certain small businesses. Orphan designated drugs are also exempt from program fees if the drug meets certain public health and revenue criteria.

The FDA conducts a preliminary review of an NDA generally within 60 calendar days of its receipt and strives to inform the sponsor by the 74th day after the FDA's receipt of the submission to determine whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review process of NDAs. Under that agreement, 90% of applications seeking approval of New Molecular Entities, or NMEs, are meant to be reviewed within ten months from the date on which the FDA accepts the NDA for filing, and 90% of applications for NMEs that have been designated for "priority review" are meant to be reviewed within six months of the filing date. For applications seeking approval of drugs that are not NMEs, the ten-month and six-month review periods run from the date the FDA receives the application. The review process and the Prescription Drug User Fee Act goal date may be extended by the FDA for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. These pre-approval inspections may cover all facilities associated with an NDA submission, including drug component manufacturing, e.g., active pharmaceutical ingredients, finished drug product manufacturing, and control testing laboratories. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications.

Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with cGCP.

In addition, as a condition of approval, the FDA may require an applicant to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, seriousness of the disease, expected benefit of the product, expected duration of treatment, seriousness of known or potential adverse events, and whether the product is a new molecular entity. REMS can include medication guides, physician communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU may include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The FDA may require a REMS before approval or post-approval if it becomes aware of a serious risk associated with use of the product. The requirement for a REMS can materially affect the potential market and profitability of a product.

The FDA is required to refer an application for a novel drug to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Expedited Programs for Serious Conditions: Fast Track, Breakthrough Therapy, Priority Review and Accelerated Approval

The FDA is authorized to designate certain products for beneficial treatment if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These expedited programs are referred to as Fast Track designation, Breakthrough Therapy designation, priority review designation, and accelerated approval. The 21st Century Cures Act, or the Cures Act, signed into law in December 2016, authorized $500 million in new funding over 9 years to help the FDA accelerate review and approval of products and bring new innovations and advances to patients faster and more efficiently. The Cures Act enhances the Agency's ability to modernize clinical trial designs and clinical outcome assessments to speed the development and review of novel medical products.

Fast Track

The FDA may designate a product for Fast Track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For Fast Track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a Fast Track product's application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a Fast Track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees. However, the FDA's time period goal for reviewing a Fast Track application does not begin until the last section of the application is submitted. In addition, the Fast Track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Breakthrough Therapy

A product may be designated as Breakthrough Therapy if it is intended, either alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to Breakthrough Therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner.

Priority Review

The FDA may designate a product for priority review if it is a product that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case- by-case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting product reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A priority designation is intended to direct overall attention and resources to the evaluation of such applications, and to shorten the FDA's goal for taking action on a marketing application from ten months to six months.

Accelerated Approval Pathway

The FDA may grant accelerated approval to a drug for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may also grant accelerated approval for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on IMM. The FDA has limited experience with accelerated approvals based on intermediate clinical endpoints, but has indicated that such endpoints generally may support accelerated approval where the therapeutic effect measured by the endpoint is not itself a clinical benefit and basis for traditional approval, if there is a basis for concluding that the therapeutic effect is reasonably likely to predict the ultimate clinical benefit of a drug.

Accelerated approval is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a drug, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. Thus, accelerated approval has been used extensively in the development and approval of drugs for treatment of a variety of cancers in which the goal of therapy is generally to improve survival or decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large trials to demonstrate a clinical or survival benefit. Thus, the benefit of accelerated approval derives from the potential to receive approval based on surrogate endpoints sooner than possible for trials with clinical or survival endpoints, rather than deriving from any explicit shortening of the FDA approval timeline, as is the case with priority review.

Accelerated approval is usually contingent on a sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the drug's clinical benefit. As a result, a drug candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, would allow the FDA to initiate expedited proceedings to withdraw approval of the drug. All promotional materials for drug candidates approved under accelerated regulations are subject to prior review by the FDA.

The FDA's Decision on an NDA

On the basis of the FDA's evaluation of the NDA and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

If the FDA approves a product, it may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess the drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing, annual program user fee requirements for any marketed products.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, suspension of the approval, or complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending NDAs or supplements to approved NDAs;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates the marketing, labeling, advertising and promotion of prescription drug products placed on the market. This regulation includes, among other things, standards and regulations for direct-to-consumer advertising, communications regarding unapproved uses, industry-sponsored scientific and educational activities, and promotional activities involving the Internet and social media. Promotional claims about a drug's safety or effectiveness are prohibited before the drug is approved. After approval, a drug product generally may not be promoted for uses that are not approved by the FDA, as reflected in the product's prescribing information. In the United States, healthcare professionals are generally permitted to prescribe drugs for such uses not described in the drug's labeling, known as off-label uses, because the FDA does not regulate the practice of medicine. However, FDA regulations impose rigorous restrictions on manufacturers' communications, prohibiting the promotion of off-label uses. It may be permissible, under very specific, narrow conditions, for a manufacturer to engage in non-promotional, non-misleading communication regarding off-label information, such as distributing scientific or medical journal information. If a company is found to have promoted off-label uses, it may become subject to adverse public relations and administrative and judicial enforcement by the FDA, the Department of Justice, or the Office of the Inspector General of the Department of Health and Human Services, as well as state authorities. This could subject a company to a range of penalties that could have a significant commercial impact, including civil and criminal fines and agreements that materially restrict the manner in which a company promotes or distributes drug products. The federal government has levied large civil and criminal fines against companies for alleged improper promotion, and has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, and its implementation regulations, as well as the Drug Supply Chain Security Act, or DSCSA, which regulate the distribution and tracing of prescription drugs and prescription drug samples at the federal level, and set minimum standards for the regulation of drug distributors by the states. The PDMA, its implementing regulations and state laws limit the distribution of prescription pharmaceutical product samples, and the DSCSA imposes requirements to ensure accountability in distribution and to identify and remove counterfeit and other illegitimate products from the market.

Abbreviated New Drug Applications for Generic Drugs

In 1984, with passage of the Hatch-Waxman Amendments to the FDCA, Congress established an abbreviated regulatory scheme allowing the FDA to approve generic drugs that are shown to contain the same active ingredients as, and to be bioequivalent to, drugs previously approved by the FDA pursuant to NDAs. To obtain approval of a generic drug, an applicant must submit an abbreviated new drug application, or ANDA, to the agency. An ANDA is a comprehensive submission that contains, among other things, data and information pertaining to the active pharmaceutical ingredient, bioequivalence, drug product formulation, specifications and stability of the generic drug, as well as analytical methods, manufacturing process validation data and quality control procedures. ANDAs are "abbreviated" because they generally do not include preclinical and clinical data to demonstrate safety and effectiveness. Instead, in support of such applications, a generic manufacturer may rely on the preclinical and clinical testing previously conducted for a drug product previously approved under an NDA, known as the reference-listed drug, or RLD.

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, the strength and the conditions of use of the drug. At the same time, the FDA must also determine that the generic drug is "bioequivalent" to the innovator drug. Under the statute, a generic drug is bioequivalent to a RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug..."

Upon approval of an ANDA, the FDA indicates whether the generic product is "therapeutically equivalent" to the RLD in its publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also referred to as the "Orange Book." Physicians and pharmacists consider a therapeutic equivalent generic drug to be fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA's designation of therapeutic equivalence often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient.

Under the Hatch-Waxman Amendments, the FDA may not approve an ANDA until any applicable period of non-patent exclusivity for the RLD has expired. The FDCA provides a period of five years of non-patent data exclusivity for a new drug containing a new chemical entity. For the purposes of this provision, a new chemical entity, or NCE, is a drug that contains no active moiety that has previously been approved by the FDA in any other NDA. An active moiety is the molecule or ion responsible for the physiological or pharmacological action of the drug substance. In cases where such NCE exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the applicant may submit its application four years following the original product approval.

The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication. Three-year exclusivity would be available for a drug product that contains a previously approved active moiety, provided the statutory requirement for a new clinical investigation is satisfied. Unlike five-year NCE exclusivity, an award of three-year exclusivity does not block the FDA from accepting ANDAs seeking approval for generic versions of the drug as of the date of approval of the original drug product. The FDA typically makes decisions about granting data exclusivity shortly before a product is approved.

505(b)(2) NDAs

As an alternative path to FDA approval for modifications to formulations or uses of products previously approved by the FDA pursuant to an NDA, an applicant may submit an NDA under Section 505(b)(2) of the FDCA. Section 505(b)(2) was enacted as part of the Hatch-Waxman Amendments and permits the filing of an NDA where at least some of the information required for approval comes from studies not conducted by, or for, the applicant. If the 505(b)(2) applicant can establish that reliance on FDA's previous findings of safety and effectiveness is scientifically and legally appropriate, it may eliminate the need to conduct certain preclinical or clinical studies of the new product. The FDA may also require companies to perform additional studies or measurements, including clinical trials, to support the change from the previously approved reference drug. The FDA may then approve the new product candidate for all, or some, of the label indications for which the reference drug has been approved, as well as for any new indication sought by the 505(b)(2) applicant.

Hatch-Waxman Patent Certification and the 30-Month Stay

Upon approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the applicant's product or an approved method of using the product. Each of the patents listed by the NDA sponsor is published in the Orange Book. When an ANDA applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval. To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would.

Specifically, the applicant must certify with respect to each patent that:

- the required patent information has not been filed;
- the listed patent has expired;
- the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or
- the listed patent is invalid, unenforceable or will not be infringed by the new product.

A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicates that it is not seeking approval of a patented method of use, the application will not be approved until all the listed patents claiming the referenced product have expired, other than method of use patents involving indications for which the applicant is not seeking approval.

If the ANDA or 505(b)(2) applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA or 505(b)(2) application has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the application until the earlier of 30 months after the receipt of the Paragraph IV notice, expiration of the patent, or a decision in the infringement case that is favorable to the applicant. The ANDA or 505(b)(2) application also will not be approved until any applicable non-patent exclusivity listed in the Orange Book for the branded reference drug has expired.

Pediatric Studies and Exclusivity

Under the Pediatric Research Equity Act, an NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. With enactment of the FDA Safety and Innovation Act of 2012 (FDASIA) , sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests, and any other information required by regulation. The applicant, the FDA, and the FDA's internal review committee must then review the information submitted, consult with each other, and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time.

In addition, the FDA Reauthorization Act of 2017 (FDARA) requires the FDA to meet early in the development process to discuss pediatric study plans with drug sponsors. The legislation requires the FDA to meet with drug sponsors by no later than the end-of-phase 1 meeting for serious or life-threatening diseases and by no later than 90 days after the FDA's receipt of the study plan.

The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in FDASIA. Unless and until the FDA promulgates a regulation stating otherwise, the pediatric data requirements do not apply to products with orphan designation.

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non-patent and orphan exclusivity. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application. With regard to patents, the six-month pediatric exclusivity period will not attach to any patents for which a generic (ANDA or 505(b)(2) NDA) applicant submitted a paragraph IV patent certification, unless the NDA sponsor or patent owner first obtains a court determination that the patent is valid and infringed by a proposed generic product.

Orphan Drug Designation and Exclusivity

Under the Orphan Drug Act, the FDA may designate a drug product as an "orphan drug" if it is intended to treat a rare disease or condition, generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a drug product available in the United States for treatment of the disease or condition will be recovered from sales of the product. A company must request orphan drug designation before submitting an NDA for that drug for that rare disease or condition. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. orphan drug designation does not shorten the PDUFA goal dates for the regulatory review and approval process, although it does convey certain advantages, such as tax benefits and exemptions from the PDUFA application and program fees.

If a product with orphan designation receives the first FDA approval for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the product generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve another sponsor's marketing application for the same drug for the same indication for seven years, except in certain limited circumstances. Orphan drug exclusivity does not block the approval of a different drug for the same rare disease or condition, nor does it block the approval of the same drug for different indications. If a drug or drug product designated as an orphan product ultimately receives marketing approval for an indication broader than what was designated on its orphan product application, it may not be entitled to exclusivity.

Under FDARA, orphan exclusivity will not bar approval of another orphan drug under certain circumstances, including if a subsequent product with the same drug for the same indication is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand. The new legislation reverses prior precedent holding that the Orphan Drug Act unambiguously required the FDA to recognize orphan exclusivity regardless of a showing of clinical superiority.

Patent Term Restoration and Extension

A patent claiming a new drug product may be eligible for a limited patent term extension, also known as patent term restriction, under the Hatch-Waxman Act, which permits a patent restoration of up to five years for patent term lost during product development and the FDA regulatory review. Patent term extension is generally available only for drug products whose active ingredient has not previously been approved by the FDA. The restoration period granted is typically one-half the time between the effective date of an IND and the submission date of an NDA, plus the time between the submission date of an NDA and the ultimate approval date. Patent term extension cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved drug product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple drugs for which approval is sought can only be extended in connection with one of the approvals. The United States PTO reviews and approves the application for any patent term extension in consultation with the FDA.

FDA Approval and Regulation of Companion Diagnostics

If safe and effective use of a therapeutic product depends on an *in vitro* diagnostic medical device, then the FDA generally will require approval or clearance of that diagnostic, known as an *in vitro* companion diagnostic device, at the same time that the FDA approves the therapeutic product. In August 2014, the FDA issued final guidance clarifying the requirements that will apply to approval of therapeutic products and *in vitro* companion diagnostic devices. According to the guidance, for novel drugs, an *in vitro* companion diagnostic device and its corresponding therapeutic should be approved or cleared contemporaneously by the FDA for the use indicated in the therapeutic product's labeling.

If the FDA determines that an *in vitro* companion diagnostic device is essential to the safe and effective use of a novel therapeutic product or indication, the FDA generally will not approve the therapeutic product or new therapeutic product indication if the *in vitro* companion diagnostic device is not approved or cleared for that indication. Approval or clearance of the *in vitro* companion diagnostic device will ensure that the device has been adequately evaluated and has adequate performance characteristics in the intended population.

Under the FDCA, *in vitro* diagnostics, including *in vitro* companion diagnostic devices, are generally regulated as medical devices. In the United States, the FDCA and its implementing regulations, and other federal and state statutes and regulations govern, among other things, medical device design and development, preclinical and clinical testing, premarket clearance or approval, registration and listing, manufacturing, labeling, storage, advertising and promotion, sales and distribution, export and import, and post-market surveillance. Unless an exemption applies, diagnostic tests require marketing clearance or approval from the FDA prior to commercial distribution. The two primary types of FDA marketing authorization applicable to a medical device are premarket notification, also called 510(k) clearance, and premarket approval, or PMA approval. The FDA has generally required *in vitro* companion diagnostic devices intended to select the patients who will respond to a drug to obtain a PMA for that diagnostic simultaneously with approval of the drug.

The PMA process, including the gathering of clinical and preclinical data and the submission to and review by the FDA, can take several years or longer. It involves a rigorous premarket review during which the applicant must prepare and provide the FDA with reasonable assurance of the device's safety and effectiveness and information about the device and its components regarding, among other things, device design, manufacturing and labeling. PMA applications are subject to an application fee, which exceeds $250,000 for most PMAs. In addition, PMAs for certain devices must generally include the results from extensive preclinical and adequate and well-controlled clinical trials to establish the safety and effectiveness of the device for each indication for which FDA approval is sought. In particular, for a diagnostic, a PMA application typically requires data regarding analytical and clinical validation studies. As part of the PMA review, the FDA will typically inspect the manufacturer's facilities for compliance with the Quality System Regulation, or QSR, which imposes elaborate testing, control, documentation and other quality assurance requirements.

PMA approval is not guaranteed, and the FDA may ultimately respond to a PMA submission with a not approvable determination based on deficiencies in the application and require additional clinical trial or other data that may be expensive and time-consuming to generate and that can substantially delay approval. If the FDA's evaluation of the PMA application is favorable, the FDA typically issues an approvable letter requiring the applicant's agreement to specific conditions, such as changes in labeling, or specific additional information, such as submission of final labeling, in order to secure final approval of the PMA. If the FDA's evaluation of the PMA or manufacturing facilities is not favorable, the FDA will deny approval of the PMA or issue a not approvable letter. A not approvable letter will outline the deficiencies in the application and, where practical, will identify what is necessary to make the PMA approvable. The FDA may also determine that additional clinical trials are necessary, in which case the PMA approval may be delayed for several months or years while the trials are conducted and then the data submitted in an amendment to the PMA. If the FDA concludes that the applicable criteria have been met, the FDA will issue a PMA for the approved indications, which can be more limited than those originally sought by the applicant. The PMA can include post-approval conditions that the FDA believes necessary to ensure the safety and effectiveness of the device, including, among other things, restrictions on labeling, promotion, sale and distribution. Once granted, PMA approval may be withdrawn by the FDA if compliance with post approval requirements, conditions of approval or other regulatory standards are not maintained or problems are identified following initial marketing.

After a device is placed on the market, it remains subject to significant regulatory requirements. Medical devices may be marketed only for the uses and indications for which they are cleared or approved. Device manufacturers must also establish registration and device listings with the FDA. A medical device manufacturer's manufacturing processes and those of its suppliers are required to comply with the applicable portions of the QSR, which cover the methods and documentation of the design, testing, production, processes, controls, quality assurance, labeling, packaging and shipping of medical devices. Domestic facility records and manufacturing processes are subject to periodic unscheduled inspections by the FDA. The FDA also may inspect foreign facilities that export products to the United States.

The 21st Century Cures Act

On December 13, 2016, President Obama signed the 21st Century Cures Act, or the Cures Act, into law. The Cures Act is designed to modernize and personalize healthcare, spur innovation and research, and streamline the discovery and development of new therapies through increased federal funding of particular programs. It authorizes increased funding for the FDA to spend on innovation projects. The new law also amends the Public Health Service Act to reauthorize and expand funding for the National Institutes of Health. The Act establishes the NIH Innovation Fund to pay for the cost of development and implementation of a strategic plan, early stage investigators and research. It also charges NIH with leading and coordinating expanded pediatric research. Further, the Cures Act directs the Centers for Disease Control and Prevention to expand surveillance of neurological diseases.

With amendments to the FDCA and the Public Health Service Act, or PHSA, Title III of the Cures Act seeks to accelerate the discovery, development, and delivery of new medicines and medical technologies. To that end, and among other provisions, the Cures Act reauthorizes the existing priority review voucher program for certain drugs intended to treat rare pediatric diseases until 2020, and requires the FDA to evaluate the potential use of "real world evidence" to help support approval of new indications for approved drugs.

The FDA Reauthorization Act of 2017

On August 18, 2017, President Trump signed the FDA Reauthorization Act of 2017 (FDARA) into law. FDARA reauthorizes the various user fees to facilitate the agency's review and oversight relating to prescription drugs, generic drugs, medical devices, and biosimilars. The legislation also includes several policy riders that will impact an array of issues within the FDA's authority including, among others, pediatric study requirements, orphan drug exclusivity, and the approval process for generic drugs.

Regulation and Procedures Governing Approval of Medicinal Products in the European Union

In addition to regulations in the United States, we will be subject to a variety of foreign regulations governing clinical trials and commercial sales and distribution of setmelanotide to the extent we choose to sell any setmelanotide outside of the United States. Whether or not we obtain FDA approval for a product, we must obtain approval of a product by equivalent competent authorities in foreign jurisdictions before we can commence clinical trials or marketing of the product in those countries. The approval process varies from country to country and the time may be longer or shorter than that required for FDA approval. The requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from country to country. As in the United States, post-approval regulatory requirements, such as those regarding product manufacture, marketing, or distribution would apply to any product that is approved outside the United States.

The process governing the marketing authorization of medicinal products in the European Union entails satisfactory completion of preclinical studies and adequate and well-controlled clinical trials to establish the safety, quality and efficacy of the medicinal product for each proposed therapeutic indication. It also requires the submission to the relevant competent authorities of a marketing authorization application, or MAA, and granting of a marketing authorization by these authorities before the product can be marketed and sold in the European Union.

Clinical Trial Approval

The Clinical Trials Directive 2001/20/EC, the Directive 2005/28/EC on Good Clinical Practice, or GCP, and the related national implementing provisions of the individual EU member states govern the system for the approval of clinical trials in the European Union. Under this system, an applicant must obtain prior approval from the competent national authority of the EU member states in which the clinical trial is to be conducted. Furthermore, the applicant may only start a clinical trial at a specific study site after the competent ethics committee has issued a favorable opinion. The clinical trial application must be accompanied by, among other documents, an investigational medicinal product dossier (the Common Technical Document) with supporting information prescribed by Directive 2001/20/EC, Directive 2005/28/EC, where relevant the implementing national provisions of the individual EU member states and further detailed in applicable guidance documents.

In April 2014, the new Clinical Trials Regulation, (EU) No 536/2014 (Clinical Trials Regulation) was adopted. The Regulation was anticipated to enter into force in 2019, but it is expected to be delayed. The Clinical Trials Regulation will be directly applicable in all the EU member states, repealing the current Clinical Trials Directive 2001/20/EC. Conduct of all clinical trials performed in the European Union will continue to be bound by currently applicable provisions until the new Clinical Trials Regulation becomes applicable. The extent to which on-going clinical trials will be governed by the Clinical Trials Regulation will depend on when the Clinical Trials Regulation becomes applicable and on the duration of the individual clinical trial. If a clinical trial continues for more than three years from the day on which the Clinical Trials Regulation becomes applicable the Clinical Trials Regulation will at that time begin to apply to the clinical trial.

The new Clinical Trials Regulation aims to simplify and streamline the approval of clinical trials in the European Union. The main characteristics of the regulation include: a streamlined application procedure via a single entry point, the "EU portal"; a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures for clinical trial sponsors; and a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts. Part I is assessed by the competent authorities of all EU member states in which an application for authorization of a clinical trial has been submitted (member states concerned). Part II is assessed separately by each member state concerned. Strict deadlines have been established for the assessment of clinical trial applications. The role of the relevant ethics committees in the assessment procedure will continue to be governed by the national law of the concerned EU member state. However, overall related timelines will be defined by the Clinical Trials Regulation.

Marketing Authorization

To obtain a marketing authorization for a product under European Union regulatory systems, an applicant must submit an MAA either under a centralized procedure administered by the EMA or one of the procedures administered by competent authorities in the EU member states (decentralized procedure, national procedure or mutual recognition procedure). A marketing authorization may be granted only to an applicant established in the European Union. Regulation (EC) No 1901/2006 provides that prior to obtaining a marketing authorization in the European Union, applicants have to demonstrate compliance with all measures included in an EMA-approved Pediatric Investigation Plan, or PIP, covering all subsets of the pediatric population, unless the EMA has granted (1) a product-specific waiver, (2) a class waiver or (3) a deferral for one or more of the measures included in the PIP. On April 27, 2018, the EMA adopted a positive opinion concerning the PIPs for setmelanotide in the treatment of appetite and general nutritional disorders. This included the deferral and the waiver requested by us

The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid for all EU member states and three of the four European Free Trade Association, or EFTA, States, Iceland, Liechtenstein and Norway. Pursuant to Regulation (EC) No 726/2004, the centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy products and products with a new active substance indicated for the treatment of certain diseases, including products for the treatment of cancer. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional.

Under the centralized procedure, the Committee for Medicinal Products for Human Use, or the CHMP, established at the EMA is responsible for conducting the initial assessment of a product. The CHMP is also responsible for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops, when additional information or written or oral explanation is to be provided by the applicant in response to questions of the CHMP. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation. If the CHMP accepts such request, the time limit of 210 days will be reduced to 150 days but it is possible that the CHMP can revert to the standard time limit for the centralized procedure if it considers that it is no longer appropriate to conduct an accelerated assessment. At the end of this period, the CHMP provides a scientific opinion on whether or not a marketing authorization should be granted in relation to a medicinal product. Within 15 calendar days of receipt of a final opinion from the CHMP, the European Commission must prepare a draft decision concerning an application for marketing authorization. This draft decision must take the opinion and any relevant provisions of EU law into account. Before arriving at a final decision on an application for centralized authorization of a medicinal product the European Commission must consult the Standing Committee on Medicinal Products for Human Use. The Standing Committee is composed of representatives of the EU member states and chaired by a non-voting European Commission representative. The European Parliament also has a related "droit de regard." The European Parliament's role is to ensure that the European Commission has not exceeded its powers in deciding to grant or refuse to grant a marketing authorization.

The EMA offers the possibility to medicinal products developers to participate in a voluntary scheme of enhanced interaction and early dialogue with the Agency, to enhance support for the development of medicinal products that target an unmet medical need. This voluntary scheme is called Priority Medicine support scheme, or PRIME. PRIME is intended to enable accelerated assessment of applications for marketing authorizations of medicinal products.

Unlike the centralized authorization procedure, the decentralized marketing authorization procedure requires a separate application to, and leads to separate approval by, the competent authorities of each EU member state in which the product is to be marketed. This application is identical to the application that would be submitted to the EMA for authorization through the centralized procedure. The reference EU member state prepares a draft assessment and drafts of the related materials within 120 days after receipt of a valid application. The resulting assessment report is submitted to the concerned EU member states who, within 90 days of receipt, must decide whether to approve the assessment report and related materials. If a concerned EU member state cannot approve the assessment report and related materials due to concerns relating to a potential serious risk to public health, disputed elements may be referred to the European Commission, whose decision is binding on all EU member states.

The mutual recognition procedure similarly is based on the acceptance by the competent authorities of the EU member states of the marketing authorization of a medicinal product by the competent authorities of other EU member states. The holder of a national marketing authorization may submit an application to the competent authority of an EU member state requesting that this authority recognize the marketing authorization delivered by the competent authority of another EU member state.

Regulatory Data Protection in the European Union

In the European Union, innovative medicinal products approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity pursuant to Directive 2001/83/EC. Regulation (EC) No 726/2004 repeats this entitlement for medicinal products authorized in accordance the centralized authorization procedure. Data exclusivity prevents applicants for authorization of generics of these innovative products from referencing the innovator's data to assess a generic (abbreviated) application for a period of eight years. During an additional two-year period of market exclusivity, a generic marketing authorization application can be submitted and authorized, and the innovator's data may be referenced, but no generic medicinal product can be placed on the European Union market until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity so that the innovator gains the prescribed period of data exclusivity, another company nevertheless could also market another version of the product if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Periods of Authorization and Renewals

A marketing authorization has an initial validity for five years in principle. The marketing authorization may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the EMA or by the competent authority of the EU member state. To this end, the marketing authorization holder must provide the EMA or the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization ceases to be valid. The European Commission or the competent authorities of the EU member states may decide, on justified grounds relating to pharmacovigilance, to proceed with one further five-year period of marketing authorization. Once subsequently definitively renewed, the marketing authorization shall be valid for an unlimited period. Any authorization which is not followed by the actual placing of the medicinal product on the European Union market (in case of centralized procedure) or on the market of the authorizing EU member state within three years after authorization ceases to be valid (the so-called sunset clause).

Orphan Drug Designation and Exclusivity

Regulation (EC) No. 141/2000, as implemented by Regulation (EC) No. 847/2000 provides that a medicinal product can be designated as an orphan drug by the European Commission if its sponsor can establish: that the product is intended for the diagnosis, prevention or treatment of (1) a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the European Union when the application is made, or (2) a life-threatening, seriously debilitating or serious and chronic condition in the European Union and that without incentives it is unlikely that the marketing of the medicinal product in the European Union would generate sufficient return to justify the necessary investment. For either of these conditions, the applicant must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the European Union or, if such method exists, the medicinal product will be of significant benefit to those affected by that condition.

Once authorized, orphan medicinal products are entitled to 10 years of market exclusivity in all EU member states and in addition a range of other benefits during the development and regulatory review process including scientific assistance for study protocols, authorization through the centralized marketing authorization procedure covering all member countries and a reduction or elimination of registration and marketing authorization fees. However, marketing authorization may be granted to a similar medicinal product with the same orphan indication during the 10-year period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if this product is safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, be reduced to six years if it can be demonstrated on the basis of available evidence that the original orphan medicinal product is sufficiently profitable not to justify maintenance of market exclusivity

Regulatory Requirements after a Marketing Authorization has been Obtained

In case an authorization for a medicinal product in the European Union is obtained, the holder of the marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products. These include:

- Compliance with the European Union's stringent pharmacovigilance or safety reporting rules must be ensured. These rules can impose post-authorization studies and additional monitoring obligations.

- The manufacturing of authorized medicinal products, for which a separate manufacturer's license is mandatory, must also be conducted in strict compliance with the applicable European Union laws, regulations and guidance, including Directive 2001/83/EC, Directive 2003/94/EC, Regulation (EC) No 726/2004 and the European Commission Guidelines for Good Manufacturing Practice. These requirements include compliance with European Union cGMP standards when manufacturing medicinal products and active pharmaceutical ingredients, including the manufacture of active pharmaceutical ingredients outside of the European Union with the intention to import the active pharmaceutical ingredients into the European Union.

- The marketing and promotion of authorized medicinal products, including industry-sponsored continuing medical education and advertising directed toward the prescribers of medicinal products and/or the general public, are strictly regulated in the European Union notably under Directive 2001/83EC, as amended, and EU member state laws.

Regulatory Procedure Governing CE marking Companion Diagnostics in the European Union

In the European Union, *in vitro* medical devices are required to conform with the essential requirements of the European Union Directive on *in vitro* diagnostic medical devices (Directive No 98/79/EC, as amended). To demonstrate compliance with the essential requirements, the manufacturer must undergo a conformity assessment procedure. The conformity assessment varies according to the type of *in vitro* diagnostic medical device. The conformity assessment of *in vitro* diagnostic medical devices can require the intervention of a Notified Body, which is an organization designated by the competent authorities of an EU member state to conduct conformity assessments. The Notified Body will issue a CE Certificate of Conformity following successful completion of a conformity assessment procedure conducted in relation to the *in vitro* diagnostic medical device and its manufacturer and their conformity with the requirements of the Directive. This Certificate entitles the manufacturer to affix the CE mark to its medical device after having prepared and signed a related EC Declaration of Conformity. For *in vitro* diagnostic medical devices which do not require the intervention of a notified body, the manufacturer can issue an EC Declaration of Conformity based on a self-assessment of the conformity of its products with the Essential Requirements laid down in the *in vitro* diagnostic medical device Directive.

Brexit and the Regulatory Framework in the United Kingdom

On June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the European Union, commonly referred to as Brexit. Thereafter, on March 29, 2017, the country formally notified the European Union of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. The withdrawal of the United Kingdom from the European Union will take effect either on the effective date of the withdrawal agreement or, in the absence of agreement, two years after the United Kingdom provides a notice of withdrawal pursuant to the E.U. Treaty. Since the regulatory framework for pharmaceutical products in the United Kingdom. covering quality, safety and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales and distribution of pharmaceutical products is derived from European Union directives and regulations, Brexit could materially impact the future regulatory regime which applies to products and the approval of product candidates in the United Kingdom. It remains to be seen how, if at all, Brexit will impact regulatory requirements for product candidates and products in the United Kingdom.

Pharmaceutical Coverage and Reimbursement

In the United States and markets in other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated healthcare costs. Patients are unlikely to use setmelanotide unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our products. Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Even if setmelanotide is approved, sales will depend, in part, on the extent to which third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations, provide coverage, and establish adequate reimbursement levels for, such products. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged, examining the medical necessity, and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable marketing approvals. Nonetheless, setmelanotide may not be considered medically necessary or cost effective. A decision by a third-party payor not to cover setmelanotide could reduce physician utilization of our products once approved and have a material adverse effect on our sales, results of operations and financial condition. Additionally, a payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage and reimbursement for the product, and the level of coverage and reimbursement can differ significantly from payor to payor. Third-party reimbursement and coverage may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

The containment of healthcare costs also has become a priority of federal, state and foreign governments and the prices of products have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit a company's revenue generated from the sale of any approved products. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which a company or its collaborators receive marketing approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Outside the United States, ensuring adequate coverage and payment for setmelanotide will face challenges. Pricing of prescription pharmaceuticals is subject to governmental control in many countries. Pricing negotiations with governmental authorities can extend well beyond the receipt of regulatory marketing approval for a product and may require us to conduct a clinical trial that compares the cost effectiveness of setmelanotide or products to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in our commercialization efforts.

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular medicinal product candidate to currently available therapies or so called Health Technology Assessments, in order to obtain reimbursement or pricing approval. For example, the European Union provides options for its member states to restrict the range of products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. EU member states may approve a specific price for a product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other EU member states allow companies to fix their own prices for products, but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions.

Healthcare Law and Regulation

Healthcare providers and third-party payors play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements and interactions with healthcare professionals, third-party payors, and patients, among others, are subject to broadly applicable fraud and abuse, anti-kickback, false claims laws, patient privacy laws and regulations and other healthcare laws and regulations that may constrain our business and/or financial arrangements, particularly once third-party reimbursement, including under Medicare, Medicaid or other federally-funded health care programs, becomes available for one or more of our products. The federal and state healthcare laws and regulations that may affect our ability to operate include, but are not limited to the following:

- the United States federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, or receiving remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, lease, order or arranging for or recommending the purchase, lease, or order of any good or service, for which payment may be made, in whole or in part, by federal healthcare programs such as Medicare and Medicaid. This statute has been interpreted to apply to arrangements between pharmaceutical companies on one hand and prescribers, purchasers and formulary managers on the other. Liability under the Anti-Kickback Statute may be established without proving actual knowledge of the statute or specific intent to violate it. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. Although there are a number of statutory exemptions and regulatory safe harbors to the federal Anti-Kickback Statute protecting certain common business arrangements and activities from prosecution or regulatory sanctions, the exemptions and safe harbors are drawn narrowly. Practices that involve remuneration to those who prescribe, purchase, or recommend pharmaceutical and biological products, including certain discounts, or engaging such individuals as consultants, advisors and speakers, may be subject to scrutiny if they do not fit squarely within an exemption or safe harbor. Our practices may not in all cases meet all of the criteria for safe harbor protection from anti-kickback liability. Moreover, there are no safe harbors for many common practices, such as educational and research grants, charitable donations, product support and patient assistance programs;

- the federal civil False Claims Act prohibits individuals or entities from, among other things, knowingly presenting, or causing to be presented, a false or fraudulent claim for payment of government funds, or knowingly making, using or causing to made or used a false record or statement material to an obligation to pay money to the government or knowingly concealing or knowingly and improperly avoiding, decreasing, or concealing an obligation to pay money to the federal government. Actions under the False Claims Act may be brought by the Attorney General or as a qui tam action by a private individual in the name of the government. Many pharmaceutical manufacturers have been investigated and have reached substantial financial settlements with the federal government under the civil False Claims Act for a variety of alleged improper activities including causing false claims to be submitted as a result of the marketing of their products for unapproved and thus non-reimbursable uses, inflating prices reported to private price publication services which are used to set drug payment rates under government healthcare programs, and other interactions with prescribers and other customers including those that may have affected their billing or coding practices and submission to the federal government. The government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. Pharmaceutical and other healthcare companies also are subject to other federal false claims laws, including, among others, federal criminal healthcare fraud and false statement statutes that extend to non-government health benefit programs;

- the federal Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, or HIPAA, which imposes criminal and civil liability for, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, or knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement or representation, or making or using any false writing or document knowing the same to contain any materially false, fictitious or fraudulent statement or entry, in connection with the delivery of or payment for healthcare benefits, items or services;

- HIPAA and its implementing regulations, which impose obligations with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

- the federal Physician Payments Sunshine Act, being implemented as the Open Payments Program requires certain manufacturers of drugs, devices, biologics and medical supplies report payments and other transfers of value to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Pharmaceutical and biological manufacturers with products for which payment is available under Medicare, Medicaid or the State Children's Health Insurance Program are required to submit a report to the Centers for Medicare and Medicaid Services within the U.S. Department of Health and Human Services on or before the 90th day of each calendar year disclosing reportable payments made in the previous calendar year; and

- analogous state laws and regulations, such as state anti-kickback and false claims laws, which may apply to healthcare items or services that are reimbursed by non-governmental third-party payors, including private insurers.

In addition to the foregoing requirements, several states now require prescription drug companies to report expenses relating to the marketing and promotion of drug products and to report gifts and payments to individual physicians in these states. Other states prohibit various other marketing-related activities, including the ability of manufacturers to offer co-pay support to patients for certain prescription drugs. Still other states require the posting of information relating to clinical studies and their outcomes and other states and cities require identification or licensing of sales representatives. In addition, California, Connecticut, Nevada, and Massachusetts require pharmaceutical companies to implement compliance programs and/or marketing codes. Several additional states are considering similar proposals. Numerous federal, state and foreign laws and regulations also govern the privacy and security of health information and the collection, use, disclosure, and protection of health-related and other personal information, including state data breach notification laws, state health information privacy laws, and federal and state consumer protection laws, such as Section 5 of the FTC Act, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts. Compliance with these laws is difficult and time consuming, and companies that do not comply with these state laws may face civil penalties.

Compliance with these federal and state laws and regulations will require substantial resources. If our operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we may be subject to significant civil, criminal and administrative penalties, imprisonment, damages, fines, imprisonment, exclusion from government-funded healthcare programs like Medicare and Medicaid, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our financial results.

For additional information regarding obligations under federal health care programs, refer to the risk factor entitled "*If we participate in the Medicaid Drug Rebate Program and fail to comply with our reporting and payment obligations under that program or other governmental pricing programs that we participate in, we could be subject to additional reimbursement requirements, penalties, sanctions and fines, which could have a material adverse effect on our business, financial condition, results of operations and growth prospects*."

In the EU, once a marketing authorization is granted for a medicinal product the applicant is required to engage in pricing and reimbursement discussions and negotiate with a separate pricing authority in each of the EU member states. The EU member states governments influence the price of pharmaceutical products through their pricing and reimbursement rules and control of national healthcare systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed upon. To obtain reimbursement or pricing approval, some of the EU member states may require the completion of clinical trials that compare the cost-effectiveness of a particular product candidate to currently available therapies. Other EU member states allow companies to fix their own prices for medicinal products, but monitor and control company profits. The downward pressure on healthcare costs in general, particularly pharmaceuticals, has become more intense. As a result, increasingly high barriers are being erected to the entry of new products. Furthermore, an increasing number of EU member states and other foreign countries use prices for medicinal products established in other countries as "reference prices" to help determine the price of the product in their own territory. Consequently, a downward trend in prices of medicinal products in some countries could contribute to similar downward trends elsewhere. The EU member states have discretion to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. An EU member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. Health Technology Assessment, or HTA, of medicinal products is becoming an increasingly common part of the pricing and reimbursement procedures in some E.U. Member States. These EU member states include the United Kingdom, France, Germany, Ireland, Italy and Sweden. The HTA process in European Economic Area, or EEA, countries is governed by the national laws of these countries. HTA is the procedure according to which the assessment of the public health impact, therapeutic impact and the economic and societal impact of use of a given medicinal product in the national healthcare systems of the individual country is conducted. HTA generally focuses on the clinical efficacy and effectiveness, safety, cost, and cost-effectiveness of individual medicinal products as well as their potential implications for the healthcare system. Those elements of medicinal products are compared with other treatment options available on the market.

Healthcare Reform

A primary trend in the United States healthcare industry and elsewhere is cost containment. There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biopharmaceutical products, limiting coverage and reimbursement for drugs and other medical products, government control and other changes to the healthcare system in the United States.

By way of example, the United States and state governments continue to propose and pass legislation designed to reduce the cost of healthcare. In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act of 2010, or collectively the ACA, which, among other things, includes changes to the coverage and payment for products under government health care programs. Among the provisions of the ACA of importance to our potential drug candidates are:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs, although this fee does not apply to sales of certain products approved exclusively for orphan indications;

- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;

- expansion of manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs and revising the definition of "average manufacturer price," or AMP, for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices and extending rebate liability to prescriptions for individuals enrolled in Medicare Advantage plans;

- introduction of a price reporting requirement for drugs that are inhaled, instilled, implanted, injected, or infused and not generally dispensed through retail community pharmacies;

- addition of more entity types eligible for participation in the Public Health Service 340B drug pricing program, or the 340B program;

- established the Medicare Part D coverage gap discount program by requiring manufacturers to provide a 50% point-of-sale-discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D;

- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;

- the Independent Payment Advisory Board, or IPAB, which has authority to recommend certain changes to the Medicare program to reduce expenditures by the program that could result in reduced payments for prescription drugs. However, the IPAB implementation has been not been clearly defined. ACA provided that under certain circumstances, IPAB recommendations or recommendations of the Secretary of Health and Human Services will become law unless Congress enacts legislation that will achieve the same or greater Medicare cost savings; and

- established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending.

Other legislative changes have been proposed and adopted in the United States since the ACA was enacted. For example, beginning April 1, 2013, Medicare payments for all items and services, including drugs and biologics, were reduced by 2% under the sequestration (i.e., automatic spending reductions) required by the Budget Control Act of 2011, as amended by the American Taxpayer Relief Act of 2012. Subsequent legislation extended the 2% reduction, on average, to 2025.

Legislative changes to or regulatory changes under the ACA have occurred in the 115th U.S. Congress and under the Trump administration. For example, the Tax Cuts and Jobs Act enacted on December 22, 2017, eliminated the shared responsibility payment for individuals who fail to maintain minimum essential coverage under section 5000A of the Internal Revenue Code of 1986, commonly referred to as the individual mandate, beginning in 2019. Additional legislative changes to and regulatory changes under the ACA remain possible, but the nature and extent of such potential additional changes are uncertain at this time. We expect that the ACA, as currently enacted or as it may be amended in the future, and other healthcare reform measures that may be adopted in the future, could have a material adverse effect on our industry generally and on our ability to successfully commercialize our product candidates, if approved.

Employees

We have leveraged skilled experts, consultants, CROs, and contractors to manage our clinical operations, under the leadership and direction of our management. We will expand our infrastructure to manage our clinical, finance and commercial operations with additional full-time employees.

We have 36 employees who are directly employed by us. Of these employees, 24 are engaged in research and development activities, 4 are engaged in pre-commercialization activities and 8 are engaged in support administration, including business development and finance. None of these employees are represented by labor unions or covered by collective bargaining agreements. We consider our relationships with these employees to be good.

Facilities

Our offices are located at a 6,830 square foot facility in Boston, Massachusetts used primarily for corporate functions. The lease for this space expires in May 2021.

Legal Proceedings

We are not currently a party to any material legal proceedings.

For additional information regarding healthcare reform, refer to the risk factor entitled *"Current and future healthcare reform legislation or regulation may increase the difficulty and cost for us and any future collaborators to obtain marketing approval of and commercialize setmelanotide and may adversely affect the prices we, or they, may obtain and may have a negative impact on our business and results of operations."*

MANAGEMENT

Executive Officers and Directors

The following table sets forth the names, ages and positions of our directors and executive officers as of June 15, 2018. Each executive officer is employed by us pursuant to a letter agreement entered into as of November 2016 except for Hunter C. Smith and Nithya Desikan, who entered into letter agreements as of July 2017. Prior to November 2016, each executive officer other than Hunter C. Smith and Nithya Desikan provided services to us pursuant to the Payroll Services Agreement, which was terminated in November 2016. Each executive officer will be elected annually and will serve until his re-election, or earlier resignation or removal. The executive officers, other than Hunter C. Smith and Nithya Desikan and directors have served as executive officers and directors of us, the LLC entity, the Predecessor Company and/or the Relamorelin Company during the periods set forth below. We refer to each of these persons as our executive officers.

Name	Age	Position(s)
Keith M. Gottesdiener, M.D.	64	Chief Executive Officer, President and Director
Hunter C. Smith	50	Chief Financial Officer and Treasurer
Nithya Desikan	39	Chief Commercial Officer
Lex H.T. Van der Ploeg, Ph.D.	63	Chief Scientific Officer
Fred T. Fiedorek, M.D.	64	Chief Medical Officer
Simon D. Kelner	45	Chief Human Resources Officer
Todd Foley(1)	46	Director
Ed Mathers(3)	58	Director
Neil Exter(1)	59	Director
Christophe R. Jean(2)	62	Director
David P. Meeker(2)(3)	63	Director and Chairman
David W.J. McGirr(2)(3)	64	Director

(1) Member of Compensation Committee.
(2) Member of Audit Committee.
(3) Member of Governance and Nominating Committee.

Keith M. Gottesdiener, M.D. | *Chief Executive Officer and President*

Dr. Gottesdiener has been Chief Executive Officer and a member of the Board since October 2011 and was chairman of the Board from that date until April 2017. He has been President since August 2017. He joined Rhythm after 16 years at Merck Research Laboratories, or Merck. Dr. Gottesdiener joined Merck in 1995 and held positions of increasing responsibility, eventually leading Merck's early clinical development across all therapeutic areas from 2001 through early 2006. From 2006 to 2011, he was a leader of Merck's late clinical development organization, first overseeing the development of Merck's infectious diseases and vaccine products through pivotal trials, registration, and life cycle management, including Gardasil™ (HPV Vaccine), Rotateq™ (rotavirus vaccine), Zostavax™ (zoster vaccine) and Isentress™ (HIV integrase inhibitor), among others. In 2008, Dr. Gottesdiener was appointed Late Stage Therapeutic Group Leader, and in that role led Merck's late stage clinical development efforts (from Phase 2 thru patent expiry) across all therapeutic areas. After Merck's merger with Schering Plough in 2009, he continued as co-head of late development. Dr. Gottesdiener received his B.A. from Harvard College and his M.D. from the University of Pennsylvania. He completed his residency and fellowship at the Brigham and Women's Hospital Beth Israel Medical Center Dana Farber Cancer Institute Children's Hospital programs. After his fellowship, Dr. Gottesdiener did postdoctoral research in the laboratory of Dr. Jack Strominger at Dana Farber Cancer Institute working on the molecular immunology of the T cell receptor. In 1986, he joined the faculty as an assistant professor at Columbia University, started an independent research laboratory with NIH RO 1 funding, focusing on gene transcription, and was Associate Clinical

Professor of Medicine at the time he left to join Merck in 1995. Dr. Gottesdiener was a director and the chief executive officer of Motus Therapeutics, Inc., with which the Company was previously affiliated ("Motus") until December 2016. Dr. Gottesdiener is currently a director of Intercept Pharmaceuticals and Rhythm Holding Company, LLC. We believe that Dr. Gottesdiener's detailed knowledge of our company, his extensive experience in the pharmaceutical industry as a senior executive, and his research work for both medical and academic institutions provide him with the qualifications to serve as director of our company.

***Hunter C. Smith** | Chief Financial Officer and Treasurer*

Mr. Smith has been Chief Financial Officer since July 2017 and Treasurer since August 2017. He has more than 25 years of global finance and management experience across multiple industries and financial disciplines, including expertise in business analysis and planning, mergers and acquisitions, capital raising and investor relations. Previously, he was Vice President, Finance and Chief Financial Officer of the Inflammation and Immunology Business Unit at Celgene Corporation from 2013 to July 2017. In this role, Mr. Smith provided finance leadership for the global launch of Otezla®, co led the integration of Receptos, Inc. following its acquisition by Celgene, and led global business planning and analysis for commercial affiliates and clinical study activities in over 16 countries. Before joining Celgene, Mr. Smith worked in roles of increasing responsibility at Bunge Limited from 1999 to 2013, including Director of Investor Relations, Chief Financial Officer—Asia, Corporate Treasurer, and Chief Financial Officer of Bunge's Sugar and Bioenergy Segment. Mr. Smith also serves as an independent director of Genessee & Wyoming Inc. and is a member of its compensation and governance committees. Mr. Smith holds an MBA in Finance from New York University's Stern School of Business and a B.A. in History, with honors, from Northwestern University.

***Nithya Desikan** | Chief Commercial Officer*

Ms. Desikan has been Chief Commercial Officer since July 2017. She has over 15 years of experience commercializing new therapies in domestic and global markets. Previously, Ms. Desikan worked at Biogen Inc., where she served most recently as Vice President and Asset Executive, from September 2016 to July 2017, overseeing global profit and loss account for TECFIDERA® and supporting the product's position as the #1 prescribed oral therapy in multiple sclerosis and from November 2015 to September 2016, building a team to support the Biogen pipeline for the clinical development of inflammatory bowel disease. Prior to that, Ms. Desikan held the role of Vice President and Program Executive from September 2014 to November 2015, where she led Biogen's Hematology business, now the Biogen spin off, Bioverativ, to drive the growth of ALPROLIX® and ELOCTATE® and the development of multiple preclinical assets. Before that, from February 2012 to September 2014, Ms. Desikan built the strategy to support the U.S. launch of ALPROLIX, Biogen's first entrant into the orphan hemophilia market. Before joining Biogen Inc., Ms. Desikan spent 12 years at Johnson & Johnson in the United States and China, supporting brands including: XARELTO®, LEVAQUIN®, TOPAMAX®, ULTRACET®, NUCYNTA®, NUCYNTA®ER and VELCADE®. Ms. Desikan holds a B.S. in Material Science Engineering, with honors, from the University of Florida.

***Lex H.T. Van der Ploeg, Ph.D.** | Chief Scientific Officer*

Dr. Van der Ploeg has been Chief Scientific Officer since October 2011. He has more than 25 years of drug development experience focused on obesity, metabolic disorders, oncology, and neurodegenerative diseases. Before joining Rhythm, he was Senior Vice President of Integrative Medicine and Translational Science at Abraxis Bioscience and Head of R&D at Abraxis Health; both companies were acquired by Celgene Corporation. Prior to that, he held R&D leadership roles at Merck directing drug development programs in metabolism, oncology, and neurodegenerative diseases as Vice President, Basic Research and Site Head, Merck Boston; Site Head, Merck San Diego; and Head, Obesity Research for Merck Rahway and Banyu, Japan. Previously, Dr. Van der Ploeg was an associate professor in the Department of Genetics and Development at Columbia University. He has received numerous awards and grants for his research and has published more than 200 peer reviewed research papers. Dr. Van der Ploeg is a named inventor on more than 50 patents and patent applications. Dr. Van der Ploeg was the Chief Scientific Officer of Motus until December 2016. He received an M.S. in Biochemistry from the University of Amsterdam and a Ph.D. in Biochemistry/Enzymology/Genetics from the University of Amsterdam/Netherlands Cancer Institute.

Fred T. Fiedorek, M.D. | *Chief Medical Officer*

Dr. Fiedorek has been Chief Medical Officer since October 2014, joining us after nearly 14 years at Bristol Myers Squibb, or BMS. He has extensive drug development experience across many therapeutic areas, ranging from early development through Phase 4 and commercial launch. Dr. Fiedorek has particular expertise in diabetes, metabolic disorders and cardiovascular disease, most recently serving as Senior Vice President, Head of Cardiovascular and Metabolic Development at BMS, where he led Phase 2 through Phase 4 global development for these therapeutic areas. Under his leadership, several new medicines achieved successful marketing authorization, including Onglyza® (saxagliptin), Farxiga™ (dapagliflozin), Eliquis® (apixaban), Myalept™ (metreleptin), Bydureon® Dual Chamber Pen, and Glucovance® (metformin/glyburide). While at BMS, Dr. Fiedorek also co led exploratory development, helping to transition compounds from discovery stage to proof of concept patient trials. In addition, Dr. Fiedorek co-directed the Clinical Science Committee charged with providing scientific, regulatory, and biostatistical review of Phase 1 through Phase 4 clinical trials; he was a member of the Medical Review Group charged with oversight of potential emerging safety signals from marketed medicines or compounds in development; and he participated in joint development committees for BMS alliances with Astra Zeneca, Pfizer, Otsuka, KAI Pharmaceuticals, Solvay, and Merck. Prior to joining BMS, Dr. Fiedorek held positions of increasing responsibility at Glaxo Wellcome in Research Triangle Park, or RTP, and was International Project Leader for a Phase 3 metabolic drug development program prior to his move to BMS. Dr. Fiedorek was the Chief Medical Officer of Motus until December 2016. Dr. Fiedorek received his B.A. from Yale University and his M.D. from Harvard Medical School. He completed residency and fellowship training in Internal Medicine and Endocrinology & Metabolism at Washington University in St. Louis, including post-doctoral research on the genetics of animal models of diabetes and obesity. He also served on the faculties at Washington University School of Medicine in St. Louis and the University of North Carolina in Chapel Hill School of Medicine, including an adjunct clinical appointment while at Glaxo Wellcome in RTP.

Simon D. Kelner | *Chief Human Resources Officer*

Mr. Kelner has been Chief Human Resources Officer since June 2018. He has over 20 years of experience serving in various human resources leadership roles across multiple industries, including with pharmaceutical companies and in the United States, Switzerland, Israel, and the United Kingdom. Previously, Mr. Kelner worked at Teva Pharmaceuticals from 2016 through 2018, where he served as Vice President, Human Resources—Global Talent Acquisition and Mobility, and developed hiring and talent engagement models. Prior to that, Mr. Kelner held roles of increasing responsibility at Merck from 2003 to 2016, and served most recently as Global Head Talent Development / Future Employment Models and Executive Director, HR Business Partner—R&D, Technology, Finance and Strategy. Mr. Kelner holds an International Executive MBA from Northwestern's Kellogg School of Management, a B.Sc. with Honors in Management Sciences from the University of Manchester Institute of Science and Technology, and a certification in Professional Human Resources Qualifications from the Chartered Institute of Personnel and Development.

Todd Foley

Mr. Foley has served as a member of our Board since July 2014. Mr. Foley is a managing director with MPM Capital, a venture capital firm, which he joined in 1999. Prior to joining MPM, Mr. Foley worked in business development at Genentech and in management consulting with Arthur D. Little. Mr. Foley currently serves as a member of the board of directors of Chiasma, Inc., Coda Therapeutics Inc., Iconic Therapeutics, Inc., Repare Therapeutics Inc., Semma Therapeutics, Inc., Switch Bio, Inc. and Tetherex Pharmaceuticals, Inc. Mr. Foley received a B.S. in chemistry from the Massachusetts Institute of Technology and an MBA from Harvard Business School. We believe that Mr. Foley's broad experience in the life sciences industry as a venture capitalist, as well as his service on the boards of directors of numerous companies provide him with the qualifications to serve as a director of our company.

Ed Mathers

Mr. Mathers has served as a member of our Board since March 2013. He has been a Partner at New Enterprise Associates, or NEA, a venture capital firm, since August 2008. Mr. Mathers currently serves on the boards of directors of Amplyx Pharmaceuticals, Inc., Envisia Therapeutics Inc., Intarcia Therapeutics, Inc., Inozyme Pharma, Inc., Liquidia Technologies, Inc., Lumos Pharma, Inc., Lumena Pharmaceuticals, Inc., Mirna Therapeutics, Inc., ObsEva SA, Ra Pharmaceuticals, Inc., Satori Pharmaceuticals Incorporated, Senti Biosciences and Synlogic, LLC, all of which are biotechnology companies. In addition, Mr. Mathers is a member of the Biotechnology Industry Organization board, the Southeast BIO board and the North Carolina State Physical and Mathematical Sciences Foundation board. Prior to joining NEA, Mr. Mathers served in various corporate development roles at MedImmune, Inc., a biotechnology company that was acquired by AstraZeneca PLC in 2007, culminating in the position of Executive Vice President, Corporate Development and Venture. In this role, he also led the company's venture capital subsidiary, MedImmune Ventures, Inc., from 2002 to 2008. Mr. Mathers was a director of MedImmune, LLC, from 2007 to 2008. From 2000 to 2002, Mr. Mathers was Vice President, Marketing and Corporate Licensing and Acquisitions at Inhale Therapeutic Systems, Inc., a biopharmaceutical company, which is now known as Nektar Therapeutics, Inc. Previously, for 15 years, Mr. Mathers was at Glaxo Wellcome, Inc., where he held sales and marketing positions of increasing responsibility. Mr. Mathers received a B.S. in chemistry from North Carolina State University. We believe that Mr. Mather's extensive experience in the life sciences industry as a venture capitalist and senior executive, as well as his service on the boards of directors of numerous biotechnology companies provide him with the qualifications to serve as a director of our company.

Neil Exter

Mr. Exter has served as a member of our Board since April 2014. He is a partner at Third Rock Ventures, where he plays an integral role in the formation, development, business strategy, and business development efforts of portfolio companies. He has more than 20 years of business development and strategic experience, facilitating the successful development and implementation of operations and collaborations across the spectrum of newly emerging and established biotech companies. Mr. Exeter is currently the interim chief operating officer of Goldfinch Bio. Prior to joining Third Rock Ventures, Mr. Exter was CBO of Alantos Pharmaceuticals and led the sale of that company to Amgen. Previously, he served as Vice President of Business Development for Millennium Pharmaceuticals. Mr. Exter is a board member of CytomX Therapeutics, Cibiem, Lotus Tissue Repair, Coridea NC1, Coridea NC2, Element Science, Goldfinch Bio, Pliant Therapeutics, Revolution Medicine, and Seventh Sense. He is a member of the Research Committee of Children's Hospital Boston, the investment committee of the Innovation Research Fund at Partners Healthcare, the board of directors of the New England Venture Capital Association, the Advisory Council of the Electrical and Computer Engineering Department at Cornell University, and the Board of Visitors of Columbia College. He holds an MBA as a Baker Scholar from Harvard Business School, an M.S. from Stanford University, and a B.S. from Cornell University. We believe that Mr. Exter's extensive experience in the life sciences industry as a venture capitalist and senior executive, as well as his service on the boards of directors of numerous biotechnology companies provide him with the qualifications to serve as a director of our company.

Christophe R. Jean

Mr. Jean has served as a member of our Board since April 2015. He is Executive Vice President of Corporate Strategy, Business Development, Alliances and M&A for the Ipsen Group, a position he assumed in 2013 after serving for 11 years in the position of Executive Vice President, Chief Operating Officer, with responsibility for all commercial operations and medical affairs worldwide as well as Ipsen's therapeutic area franchises. Prior to joining Ipsen, Mr. Jean was President and CEO for the pharmaceutical activities of the Pierre Fabre Group and President of Europe, Middle East, and Africa for Novartis' Pharmaceutical Division. Prior to the merger of Ciba Geigy and Sandoz that formed Novartis, he held a number of marketing and management positions in Europe and Latin America for Ciba Geigy, culminating as Head of Finance and IT Worldwide and Member of the Pharma Executive Committee. Mr. Jean is a member of the Ipsen Executive Leadership Team, the Supervisory Board of Keosys, and the European Biopharmaceutical Enterprises Board. He holds an MBA from Harvard Business School. We believe that Mr. Jean's extensive experience in the life sciences industry as a senior executive provides him with the qualifications to serve as a director of our company.

David P. Meeker

Dr. Meeker has served as a member of our Board since November 2015 and became Chairman of the Board in April 2017. Mr. Meeker currently serves as CEO of KSQ Therapeutics, Inc., a position he has held since October 2017. From October 2011 until June 2017, Dr. Meeker served as President and Chief Executive officer of Genzyme, a unit of Sanofi, a global biotechnology company. Dr. Meeker oversaw the company's two business units—Rare Diseases and Multiple Sclerosis. As an Executive Vice President of Sanofi, he was a member of Sanofi's Executive Committee. Dr. Meeker joined Genzyme in 1994 as Medical Director to work on the Cystic Fibrosis Gene Therapy program. Subsequently, as Vice President, Medical Affairs, he was responsible for the development of rare disease therapies that today represent transformative and life-saving advancements in medicine for patients. Prior to Genzyme's merger with Sanofi in 2011, Dr. Meeker was Genzyme's Chief Operating Officer, responsible for its commercial organization, overseeing its business units, country management organization and global market access functions. He played an important role in the integration with Sanofi. Prior to joining Genzyme, Dr. Meeker was the director of the Pulmonary Critical Care Fellowship at the Cleveland Clinic and an assistant professor of medicine at Ohio State University. Dr. Meeker is currently a member of the board of directors of MyoKardia, Inc. He has authored more than 40 articles and multiple book chapters. Dr. Meeker received his M.D. from the University of Vermont Medical School. He completed the Advanced Management Program at Harvard Business School in 2000. We believe that Dr. Meeker's deep experience as a senior executive at global pharmaceutical companies and involvement in the development and commercialization of pharmaceutical product candidates for the treatment of rare and ultra-rare diseases provide him with the qualifications to serve as a director of our company.

David W.J. McGirr

Mr. McGirr has served as a member of our Board since November 2015. Mr. McGirr serves as a director of Arsanis, Inc., a clinical-stage biopharmaceutical company focused on applying monoclonal antibody immunotherapies to address serious infectious diseases, Menlo Therapeutics, Inc., a late-stage biopharmaceutical company focused on an NK-1 receptor antagonist for the treatment of pruritus and for refractory chronic cough, and Insmed Incorporated, a pharmaceutical company devoted to the treatment of rare diseases. From March 2013 until June 2014, Mr. McGirr was Senior Advisor to the chief executive officer of Cubist Pharmaceuticals and from November 2002 to March 2013, Mr. McGirr was Senior Vice

President and Chief Financial Officer of Cubist. Prior to joining Cubist in 2002, Mr. McGirr was the President and Chief Operating Officer of hippo inc., an internet technology, venture-financed company. Mr. McGirr served as a member of hippo's board of directors from 1999 to 2003. From 1996 to 1999, he was the President of GAB Robins North America, Inc., a risk management company, serving also as Chief Executive Officer from 1997 to 1999. Mr. McGirr was a private equity investor from 1995 to 1996. From 1978 to 1995, Mr. McGirr served in various positions within the S.G. Warburg Group, ultimately as Chief Financial Officer, Chief Administrative Officer and Managing Director of S.G. Warburg & Co., Inc., a position he held from 1992 to 1995. Mr. McGirr received a B.Sc. in Civil Engineering from the University of Glasgow and received an M.B.A. from The Wharton School at the University of Pennsylvania. Mr. McGirr has been designated an audit committee financial expert as defined in applicable SEC rules. We believe that Mr. McGirr's senior-level executive experience in a variety of industries, including in the life sciences industry, provides him with the qualifications to serve as a director of our company.

Director Independence

Under Nasdaq rules, a majority of a listed company's board of directors must be comprised of independent directors. In addition, Nasdaq rules require that, subject to specified exceptions, each member of a listed company's audit committee and compensation committee be independent and satisfy additional independence criteria set forth in Rules 10A-3 and 10C-1, respectively, under the Securities Exchange Act of 1934, as amended, or the Exchange Act. Under Nasdaq rules, a director will only qualify as an "independent director" if, in the opinion of that company's board of directors, that person does not have a relationship that would interfere with the exercise of independent judgment in carrying out the responsibilities of a director.

Based upon information requested from and provided by each director concerning their background, employment and affiliations, including family relationships, our Board has determined, upon the recommendation of our Governance and Nominating Committee, that each of our directors other than Keith M. Gottesdiener, our President and Chief Executive Officer, has no relationship that would interfere with the exercise of independent judgment in carrying out the responsibilities of a director and is independent within the meaning of the director independence standards of the Nasdaq rules and the SEC. Our Board has also determined that each of the current members of our Audit Committee and our Compensation Committee as set forth in the "Board Committees" section below satisfies the independence standards for such committee. In making such determination, our Board considered the relationships that each such non-employee director has with Rhythm and all other facts and circumstances deemed relevant in determining their independence, including Christophe R. Jean's role as executive vice president at Ipsen Pharma SAS, an entity with which we have an ongoing contractual relationship.

Certain members of our Board were elected in compliance with the provisions of a voting agreement among us and our major stockholders. The voting agreement terminated upon the closing of our IPO, and at present we do not have any contractual obligations regarding the election of our directors. See "*Transactions with Related Persons*." There are no family relationships among any of our directors or executive officers.

Board Meetings, Attendance and Executive Sessions

The Board held six meetings and took action by written consent twice during the year ended December 31, 2017. With the exception of Christophe R. Jean, all board members attended at least 75% of the meetings of the Board and the committees of the Board on which he served (in each case, which were held during the period for which he was a director and/or a member of the applicable committee). Christophe R. Jean attended 70% of the meetings of the Board and the committees of the Board on which he served (which were held during the period for which he was a director and/or a member of the applicable committee).

Executive sessions, or meetings of the outside (non-management) directors without management present, are held regularly. The non-management directors met in executive session during each of the regularly scheduled Board meetings during the year ended December 31, 2017.

Rhythm encourages its directors to attend the Annual Meeting of Stockholders.

Board Composition and Structure

Our certificate of incorporation and bylaws, each as currently amended and in effect, state that our Board shall consist of a number of directors that shall be fixed exclusively by the Board from time to time in accordance with the bylaws of the Company. Each director holds office until his or her successor is duly elected and qualified or until his or her death, incapacity, resignation or removal. Our certificate of incorporation provides that our directors may be removed only for cause by the affirmative vote of the holders of at least 75% of the voting power of the outstanding shares of capital stock of Rhythm entitled to vote in the election of directors, voting together as a single class, at a meeting of the stockholders called for that purpose. Any vacancy in the Board, including a vacancy that results from an increase in the number of directors, may be filled only by the vote of a majority of the remaining directors then in office, although less than a quorum, or by the sole remaining director.

Our certificate of incorporation, as currently amended and in effect, provides that our Board is divided into three classes of directors, with the classes as nearly equal in number as possible. Each of our directors identified below serves in the class indicated. Subject to any earlier resignation or removal in accordance with the terms of our certificate of incorporation and bylaws, our current Class I directors will serve until the 2021 annual meeting of stockholders; our current Class II directors will serve until the 2019 annual meeting of stockholders; and our current Class III directors will serve until the 2020 annual meeting of stockholders. Any additional directorships resulting from an increase in the number of directors will be apportioned by our Board among the three classes as equally as possible.

Our Board is currently comprised of seven members. In consultation with the Governance and Nominating Committee, the Board has determined that the classified board structure is appropriate for the Company, particularly following its initial public offering. A classified board provides for stability, continuity and experience among our Board. Further, the Board believes that building a cohesive Board is an important goal. In our industry in particular, long-term focus is critical. The time horizon required for successful development of pharmaceuticals makes it vital that we have a board that understands the implications of this process and has the ability to develop and implement long-term strategies while benefiting from an in-depth knowledge of Rhythm's business and operations. A classified board structure helps to ensure that there will be the continuity and stability of leadership required to navigate a challenging economic environment while resisting the pressure to focus on short-term results at the expense of the long-term value and success of the Company. The future success of Rhythm depends in significant part on the ability to attract and retain capable and experienced directors. In this regard, we believe that longer terms for our directors will enhance director independence from both management and stockholder special interest groups.

Board Leadership Structure

The positions of chairman of the board and chief executive officer are presently separated. Our Board recognizes the time, effort and energy that the chief executive officer is required to devote to his position in the current business environment, as well as the commitment required to serve as our chairman, particularly as the board of directors' oversight responsibilities continue to grow. Our Board believes that having separate positions is the appropriate leadership structure for us at this time and demonstrates our commitment to good corporate governance.

Board Committees

Our Board has established the following committees: an Audit Committee, a Compensation Committee, and a Governance and Nominating Committee. The composition and responsibilities of each committee are described below. Members will serve on these committees until their resignation or until otherwise determined by our Board. Each of the Audit Committee, Compensation Committee, and Governance and Nominating Committee operates pursuant to a written charter and each committee reviews and assesses the adequacy of its charter annually and submits its charter to the Board for approval. The charters for the Audit Committee, Compensation Committee, and Governance and Nominating Committee are all available on our website at www.rhythmtx.com under "Investors & Media" at "Corporate Governance."

The following table describes which directors serve on each of the Board committees and includes the class for each director.

Name:	Governance and Nominating Committee	Compensation Committee	Audit Committee	Class
Neil Exter		X		II
Todd Foley		X		II
Keith M. Gottesdiener				I
Christophe R. Jean			X	I
Ed Mathers	X			II
David W. J. McGirr	X		X	III
David P. Meeker	X		X	III

Audit Committee

Our Audit Committee provides oversight of our accounting and financial reporting process, the audit of our financial statements and our internal control function. Among other matters, the Audit Committee is responsible for the following: assisting the Board in oversight of the independent auditors' qualifications, independence and performance; the engagement, retention and compensation of the independent auditors; reviewing the scope of the annual audit; reviewing and discussing with management and the independent auditors the results of the annual audit and the review of our quarterly financial statements, including the disclosures in our annual and quarterly reports filed with the SEC; reviewing our risk assessment and risk management processes; establishing procedures for receiving, retaining and investigating complaints received by us regarding accounting, internal accounting controls or audit matters; and approving audit and permissible non-audit services provided by our independent auditor.

The current members of our Audit Committee are David W.J. McGirr, who is the chair of the Audit Committee, Christophe R. Jean, and David P. Meeker. All members of our Audit Committee meet the requirements for financial literacy under the applicable rules and regulations of the SEC and Nasdaq. Our Board has determined that David W.J. McGirr is an audit committee financial expert as defined under the applicable rules of the SEC and has the requisite financial sophistication as defined under the applicable rules and regulations of Nasdaq. All of the members of our Audit Committee are independent directors as defined under the applicable rules and regulations of the SEC and Nasdaq.

During the year ended December 31, 2017, the Audit Committee met four times.

Compensation Committee

Our Compensation Committee adopts and administers the compensation policies, plans and benefit programs for our executive officers and all other members of our executive team. Our Compensation Committee is also responsible for making recommendations regarding non-employee director compensation to the full Board. In addition, among other things, our Compensation Committee evaluates annually, in consultation with the Board, the performance of our chief executive officer, reviews and approves corporate goals and objectives relevant to compensation of our chief executive officer and other executives and evaluates the performance of these executives in light of those goals and objectives. Our Compensation Committee also adopts and administer our equity compensation plans. The current members of our Compensation Committee are Neil Exter, who is the chair of the Compensation Committee, and Todd Foley. All of the members of our Compensation Committee are independent under the applicable rules and regulations of the SEC and Nasdaq.

During the year ended December 31, 2017, the Compensation Committee met two times.

Governance and Nominating Committee

Our Governance and Nominating committee is responsible for, among other things, making recommendations regarding corporate governance, the composition of our Board, the identification, evaluation and nomination of director candidates and the structure and composition of committees of our Board. In addition, our Governance and Nominating committee oversees our corporate governance guidelines, approves our committee charters, oversees compliance with our code of business conduct and ethics, contributes to succession planning, reviews policies and procedures with respect to our related party transactions policy and oversees our board self-evaluation process. The current members of our Governance and Nominating committee are David P. Meeker, who is the chair of the Governance and Nominating Committee, Ed Mathers, and David W.J. McGirr. All of the members of our Governance and Nominating committee are independent under the applicable rules and regulations of Nasdaq.

During the year ended December 31, 2017, the Governance and Nominating committee did not meet.

Compensation Committee Interlocks and Insider Participation

During the last completed fiscal year Neil Exter and Todd Foley served on the Compensation Committee. None of the members of our Compensation Committee has at any time during the prior fiscal year been one of our officers or employees. None of the members of the Compensation Committee during the prior fiscal year were formerly one of our officers. None of our executive officers currently serves, or in the past fiscal year has served, as a member of the Board or Compensation Committee of any entity that has one or more executive officers serving on our Board or Compensation Committee. For a description of transactions between us and members of our Compensation Committee and affiliates of such members, please see "*Transactions with Related Pers*ons."

The Board of Directors' Role in Risk Oversight

The audit committee of the Board, or the Audit Committee, is primarily responsible for overseeing our risk management processes on behalf of the Board. The Audit Committee receives reports from management regarding our assessment of risks. In addition, the Audit Committee reports regularly to the Board, which also considers our risk profile. The Audit Committee and the Board focus on the most significant risks we face and our general risk management strategies. While the Board oversees our risk management, management is responsible for day-to-day risk management processes. Our Board expects management to consider risk and risk management in each business decision, to proactively develop and monitor risk management strategies and processes for day-to-day activities and to effectively implement risk management strategies adopted by the Audit Committee and the Board. We believe this division of responsibilities is the most effective approach for addressing the risks we face and that the leadership structure of our Board, which also emphasizes the independence of the Board in its oversight of its business and affairs, supports this approach.

Scientific Advisory Board

Our management team is supported by a scientific advisory board composed of leading academic and industry scientists. This group generally meets quarterly with our management team either as a group or individually to provide advice and guidance on our development programs. Our scientific advisory board consists of:

John Amatruda, M.D.	Dr. Amatruda has broad clinical development expertise in metabolic disease. Most recently, he was Senior Vice President and Franchise Head for Diabetes and Obesity at Merck & Co., Inc.
Michael Camilleri, M.D.	Dr. Camilleri is a Professor of Medicine and Physiology in the Mayo Clinic College of Medicine. He is a leading expert in gastroenterology, with a research focus on enteric neurosciences and the physiology, pathophysiology, and treatment of diseases that affect gastrointestinal motility, including gastroparesis, diabetes, obesity, and irritable bowel syndrome.
William Chin, M.D.	Dr. Chin is Chief Medical Officer and Executive Vice President at PhRMA. Formerly, he was Executive Dean for Research at Harvard Medical School, following a 10-year career at Eli Lilly and Company, where he was most recently Senior Vice President for Discovery Research and Clinical Investigation.
Lee Kaplan, M.D., Ph.D. *Chairman*	Dr. Kaplan is Director of the Obesity, Metabolism, & Nutrition Institute and was Founding Director of the Weight Center at the Massachusetts General Hospital. He is an Associate Professor of Medicine at Harvard Medical School.
Elizabeth Stoner, M.D.	Dr. Stoner is a founder of the LLC entity and served as our Chief Development Officer from 2010 through 2014. Dr. Stoner previously served in various roles at Merck, most recently as Senior Vice President of Global Clinical Development Operations, and is a Managing Director at MPM Capital.

Code of Business Conduct and Ethics and Corporate Governance Guidelines

We have adopted a code of business conduct and ethics that applies to all of our employees, including our executive officers, and directors, and those employees responsible for financial reporting. The code of business conduct and ethics is available on our website. We expect that, to the extent required by law, any amendments to the code, or any waivers of its requirements, will be disclosed on our website at www.rhythmtx.com under "Investors & Media" at "Corporate Governance" or by requesting a copy, free of charge, in writing from our Secretary at Rhythm Pharmaceuticals, Inc., 500 Boylston Street, 11th Floor, Boston, MA 02116. We intend to post on our website any amendment to, or waiver under, a provision of the code of business conduct and ethics that applies to certain of our executive officers within four business days following the date of such amendment or waiver.

A copy of our corporate governance guidelines may also be accessed free of charge by visiting the website at www.rhythmtx.com under "Investors & Media" at "Corporate Governance" or by requesting a copy from our Secretary at our principal executive offices above.

EXECUTIVE AND DIRECTOR COMPENSATION

This section discusses the material elements of compensation for our named executive officers and the most important factors relevant to an analysis of these policies. It provides qualitative information regarding the manner and context in which compensation is awarded to and earned by our executive officers named in the "Summary Compensation Table" below, or our named executive officers, and is intended to place in perspective the data presented in the following tables and the corresponding narrative.

Summary Compensation Table

The following table sets forth information about compensation awarded or paid to our named executive officers for the 2016 and 2017 fiscal years.

Name and Principal Position	Year	Base Salary(1) ($)	Bonus ($)	Option Awards(2) ($)	Non-Equity Incentive Plan Compensation(3) ($)	All Other Compensation ($)	Total ($)
Keith M. Gottesdiener, M.D.,	2017	$ 490,795	—	$ 799,994	$ 245,398	—	$ 1,536,187
President and Chief Executive Officer, Director	2016	$ 476,500	—	—	$ 85,770	—	$ 562,270
Hunter C. Smith(4), *Chief Financial Officer*	2017	$ 159,795	—	$ 832,497	$ 70,490	$ 27,495	$ 1,090,277
Nithya Desikan(5), *Chief Commercial Officer*	2017	$ 158,100	$ 100,000	$ 832,497	$ 66,780	—	$ 1,157,377

(1) Salaries include amounts contributed by the named executive officer to our 401(k) plan.

(2) Amounts shown reflect the grant date fair value of options awarded during each of fiscal year 2016 and 2017, determined in accordance with the Financial Accounting Standards Board, Accounting Standards Codification Topic 718, *Compensation—Stock Compensation*. These amounts exclude the value of estimated forfeitures. Note that the amounts reported in this column reflect the accounting cost for these stock options, and do not correspond to the actual economic value that may be received by the named executive officers from the options.

(3) Amounts shown reflect the cash performance bonus amount paid to the named executive officer for fiscal years 2016 and 2017 that was earned based on Rhythm's performance. Annual cash incentive compensation earned during the year is typically paid in the following year.

(4) Mr. Smith's first day of employment was July 31, 2017.

(5) Ms. Desikan's first day of employment was July 24, 2017.

Our executive compensation program is based on a pay-for-performance philosophy. The Compensation Committee designed our executive compensation program to achieve the following primary objectives: provide compensation and benefit levels that will attract, retain, motivate and reward a highly talented executive team within the context of responsible cost management; establish a direct link between our individual/team performance and results and our executives' compensation; and align the interests and objectives of our executives with those of our stockholders by linking executive equity awards to stockholder value creation. The compensation program for our executive officers is composed primarily of the following three main components: base salary, annual cash incentives and long-term equity incentives.

Base Salary

The 2017 base salaries, effective January 1, 2017 for Mr. Gottesdiener, July 31, 2017 for Mr. Smith, and July 24, 2017 for Ms. Desikan, were determined for each named executive officer by the Compensation

Committee, which gives consideration to each officer's experience, expertise and performance, as well as market compensation levels for similar positions.

Name	2017 Base Salary ($)
Keith M. Gottesdiener, M.D., *President and Chief Executive Officer*	$ 490,795
Hunter C. Smith, *Chief Financial Officer*(1)	$ 380,000
Nithya Desikan, *Chief Commercial Officer*(2)	$ 360,000

(1) Mr. Smith was hired on July 31, 2017 and his base salary was prorated to $159,795.
(2) Ms. Desikan was hired on July 24, 2017 and her base salary was prorated to $158,100.

Annual Performance-Based Incentive Opportunity

In addition to base salaries, our named executive officers are eligible to receive annual performance-based cash incentives, which are designed to motivate our executives to achieve defined annual corporate goals and to reward our executives for their contributions towards achievement of these goals. The annual performance-based incentive each named executive officer was eligible to receive in 2017 was generally based on the extent to which the officer contributed to the achievement of the corporate goals that the Compensation Committee established at the beginning of 2017. After the end of 2017, the Compensation Committee reviewed performance against each goal and determined the extent to which each goal was achieved.

The Compensation Committee generally considered each named executive officer's individual contributions towards reaching the annual corporate goals but did not establish specific individual goals for each of them. Pursuant to the terms of their respective agreements governing their employment relationship, described below under "Employment Agreements," Dr. Gottesdiener was eligible to receive a target bonus of up to 50% of his base salary, Mr. Smith was eligible to receive a target bonus of up to 35% of his base salary, and Ms. Desikan was eligible to receive a target bonus of up to 35% of her base salary. However, there is no minimum bonus percentage or amount established for the named executive officers and, as a result, the bonus amounts have varied from year to year based on corporate and individual performance.

In December 2017, the Compensation Committee reviewed the 2017 corporate goals and based on the Compensation Committee's determination of achievement of the goals, the Compensation Committee awarded each of our named executive officers eligible for performance bonuses 100% of their target bonus opportunity for 2017. For 2017, Dr. Gottesdiener received a bonus of $245,398, Mr. Smith received a prorated bonus of $70,490, and Ms. Desikan received a prorated bonus of $66,780.

Outstanding Equity Awards at End of 2017

The following table provides information about outstanding equity awards held by each of our named executive officers at December 31, 2017. All options were granted under our 2015 equity incentive plan.

	Option Awards(1)			
Name	Number of Securities Underlying Unexercised Options (#) Exercisable	Number of Securities Underlying Unexercised Options (#) Unexercisable	Option Exercise Price ($)	Option Expiration Date
Keith M. Gottesdiener, M.D.	25,391(2)(3)	102,389	$ 4.59	11/16/2025
	34,597(2)(3)	22,655	$ 7.52	12/30/2025
	40,896(3)(4)	122,680	$ 6.14	4/4/2027
	13,632(3)(4)	40,893	$ 6.14	4/4/2027
Hunter C. Smith	—(5)	201,744	$ 6.88	8/8/2027
Nithya Desikan	32,715(6)	169,029	$ 6.88	8/8/2027

(1) Upon an option holder's termination of employment on account of the option holder's death or disability, these options expire on the first anniversary of the option holder's termination. If an option holder's employment terminates for any other reason, these options expire three months after the option holder's termination.

(2) These options vest in 48 equal monthly installments, starting on August 3, 2015, except that the last installment, if necessary, may be smaller.

(3) If the option holder's employment is terminated within the three months preceding or the 12 months immediately following a change of control of us, 100% of the option holder's equity awards will become immediately exercisable.

(4) These options vest in 48 equal monthly installments, starting on January 6, 2017, except that the last installment, if necessary, may be smaller.

(5) 50,436 of these options vest on July 31, 2018, and the remaining options vest in 36 monthly installments, starting on August 31, 2018, except that the last installment, if necessary, may be smaller.

(6) 42,257 of these options vest on July 24, 2018, and the remaining options vest in 36 monthly installments, starting on August 24, 2018, except that the last installment, if necessary, may be smaller.

Pension Benefits

Our named executive officers did not participate in, or otherwise receive any benefits under, any pension or retirement plan during 2017, other than pursuant to the 401(k) plan described under "401(k) Plan."

Nonqualified Deferred Compensation

Our named executive officers did not participate in, or earn any benefits under, a nonqualified deferred compensation plan during 2017.

Employment Agreements and Potential Payments Upon Termination or Change of Control

Below are written descriptions of our employment agreements with each of our named executive officers. Regardless of the manner in which a named executive officer's employment terminates, each named executive officer is entitled to receive amounts earned during his term of employment, including salary and unused vacation pay. In addition, each of our named executive officers is eligible to receive certain benefits pursuant to his letter agreement as described below.

Agreement with Dr. Gottesdiener. Under Dr. Gottesdiener's letter agreement, he is entitled to a base salary of $490,795, subject to adjustment in the Compensation Committee's sole discretion, is eligible to receive an annual target performance bonus of up to 50% of his base salary, as determined by the Compensation Committee, and is entitled to certain severance benefits as described below.

Upon Termination without "cause" or for "good reason" within the three months immediately preceding or the 12 months immediately following a "change of control" as defined in the letter agreement, subject to customary conditions, including his execution and nonrevocation of an acceptable release, Dr. Gottesdiener, in lieu of the above benefits, will be entitled to receive a severance payment in an aggregate amount equal to 18 months of his base salary then in effect, paid in substantially equal installments over a period of 18 months, as applicable, in accordance with ordinary payroll practices, a payment equal to 100% of his annual target bonus for the year in which the termination occurs, and reimbursement of his COBRA premiums for up to 18 months. In addition, each unvested equity award held by Dr. Gottesdiener granted by both us or the LLC entity will immediately become fully vested.

Upon Termination without "cause" or for "good reason" unrelated to a "change of control" as defined in the letter agreement, subject to customary conditions, including his execution and nonrevocation of an acceptable release, Dr. Gottesdiener, in lieu of the above benefits, will be entitled to receive a severance payment in an aggregate amount equal to 12 months of his base salary then in effect, paid in substantially equal installments over a period of 12 months, as applicable, in accordance with ordinary payroll practices.

Agreement with Mr. Smith. Under Mr. Smith's letter agreement, he is entitled to a base salary of $380,000, prorated for Mr. Smith's hire date of July 31, 2017 and subject to adjustment in the Compensation Committee's sole discretion, is eligible to receive an annual target performance bonus of up to 35% of his base salary, prorated for Mr. Smith's hire date of July 31, 2017, as determined by the Compensation Committee, and is entitled to certain severance benefits as described below.

Upon Termination without "cause" or for "good reason" within the three months immediately preceding or the 12 months immediately following a "change of control" as defined in the letter agreement, subject to customary conditions, including his execution and nonrevocation of an acceptable release, Mr. Smith, in lieu of the above benefits, will be entitled to receive a severance payment in an aggregate amount equal to 12 months of his base salary then in effect, paid in substantially equal installments over a period of 12 months, as applicable, in accordance with ordinary payroll practices, a payment equal to 100% of his annual target bonus for the year in which the termination occurs, and reimbursement of his COBRA premiums for up to 18 months. In addition, each unvested equity award held by Mr. Smith granted by us will immediately become fully vested.

Upon Termination without "cause" or for "good reason" unrelated to a "change of control" as defined in the letter agreement, subject to customary conditions, including his execution and nonrevocation of an acceptable release, Mr. Smith, in lieu of the above benefits, will be entitled to receive a severance payment in an aggregate amount equal to (i) 9 months of his base salary then in effect, paid in substantially equal installments over a period of 9 months, or (ii) 12 months of his base salary then in effect, paid in substantially equal installments over a period of 12 months, if such termination occurs prior to July 31, 2018, in each case as applicable, in accordance with ordinary payroll practices.

Agreement with Ms. Desikan. Under Ms. Desikan's letter agreement, she is entitled to a base salary of $360,000, subject to adjustment in the Compensation Committee's sole discretion, is eligible to receive an annual target performance bonus of up to 35% of her base salary, as determined by the Compensation Committee, and is entitled to certain severance benefits as described below.

Upon Termination without "cause" or for "good reason", within the three months immediately preceding or the 12 months immediately following a "change of control" as defined in the letter agreement, subject to customary conditions, including her execution and nonrevocation of an acceptable release, Ms. Desikan, in lieu of the above benefits, will be entitled to receive a severance payment in an aggregate amount equal to 12 months of her base salary then in effect, paid in substantially equal installments over a period of 12 months in accordance with ordinary payroll practices, and a payment equal to 100% of her annual target bonus for the year in which the termination occurs. In addition, each unvested equity award held by Ms. Desikan granted by us will immediately become fully vested.

Upon Termination without "cause" or for "good reason" unrelated to a "change of control" as defined in the letter agreement, subject to customary conditions, including her execution and nonrevocation of an acceptable release, Ms. Desikan, in lieu of the above benefits, will be entitled to receive a severance payment in an aggregate amount equal to (i) 9 months of her base salary then in effect, paid in substantially equal installments over a period of 9 months, or (ii) 12 months of her base salary then in effect, paid in substantially equal installments over a period of 12 months, if such termination occurs prior to July 24, 2018, in each case as applicable, in accordance with ordinary payroll practices.

For purposes of these letter agreements, "cause" generally means the occurrence of any of the following events by the individual: (i) commission of any crime involving fraud, breach of trust, or physical or emotional harm to any person, moral turpitude or dishonesty; (ii) any unauthorized use or disclosure of proprietary information (other than any such use or disclosure that is not intentional and is not material); (iii) any intentional misconduct or gross negligence that has a material adverse effect on business or reputation; (iv) any material breach by the executive of any agreement that is not cured within 30 days after receipt of notice; or (v) repeated and willful failure to perform the duties, functions and responsibilities of his position after a written warning from us.

For purposes of the letter agreements, "good reason" generally means resignation by the executive from all positions if, without the executive's written consent, there is a (i) material diminution of duties or authority; (ii) material reduction of the executive's base salary not pursuant to a program affecting all or substantially all employees unless the executive is affected to a greater extent than other similarly situated employees pursuant to such a program; or (iii) requirement to relocate the primary work location to a location that would increase the one way commute distance by more than 35 miles from the executive's primary work location as of immediately prior to such change, in each case, provided that the executive provides written notice within 30 days following such event, and failure to remedy the event within 30 days following receipt of such notice and the executive's resignation is effective no more than 30 days following the expiration of a cure period. Good reason may also occur if the executive resigns from all positions on the one-year anniversary of a change in control if the executive has not entered into a written letter or agreement providing for the executive's continued employment with us or our successor.

Compensation Consultant

In connection with our executive compensation review, in 2017 our Compensation Committee engaged Radford, an Aon Hewitt company, or Radford, an independent executive compensation consultant, to provide our Compensation Committee guidance with respect to the development and implementation of our compensation programs.

Our Compensation Committee charter requires that its compensation consultant be independent of Rhythm management. During 2017, Radford did not provide services to us other than the services described in this registration statement. Our Compensation Committee has determined that Radford is independent and that its work has not raised any conflict of interest.

Employee Benefit and Stock Plans

2017 Equity Incentive Plan

The following summary of the material terms of the 2017 Plan does not purport to be complete and is qualified by reference to the full text of the 2017 Plan.

The 2017 Plan provides for the grant of incentive stock options and nonstatutory stock options, stock appreciation rights, restricted stock and restricted stock unit awards, performance units, stock grants and qualified performance-based awards (that is, any of the foregoing that are intended to constitute performance-based compensation under Section 162(m) of the Code), which we collectively refer to as "awards" in connection with the 2017 Plan. Our directors, officers and other employees, as well as others performing consulting or advisory services for us, are eligible for grants under the Plan. The purpose of the Plan is to provide incentives that will attract, retain and motivate highly competent officers, directors, employees and consultants and advisors to promote the success of our business and align employees' interests with stockholders' interests.

Administration

Under its terms, the 2017 Plan is administered by the compensation committee of our board of directors which is made up of independent outside non-employee directors for purposes of applicable securities and tax laws. The board of directors itself may also exercise any of the powers and responsibilities under the 2017 Plan. The compensation committee may delegate to an executive officer or officers the authority to grant awards under the 2017 Plan subject to applicable law and to guidelines specified by the compensation committee. Subject to the terms of the Plan, the compensation committee will select the recipients of awards and determine, among other things, the:

- number of shares of common stock covered by awards and the dates upon which such awards become exercisable or any restrictions to which they are subject lapse, as applicable;
- type of award and the exercise or purchase price and method of payment for each such award;
- vesting period for awards, risks of forfeiture and any potential acceleration of vesting or lapses in risks of forfeiture; and
- duration of awards.

All decisions, determinations and interpretations made in good faith by the compensation committee with respect to the 2017 Plan and the terms and conditions of or operation of any award are final and binding on all participants, beneficiaries, heirs, assigns or other persons holding or claiming rights under the 2017 Plan or any award.

Available Shares

Subject to the following sentence, the aggregate number of shares of our common stock which may be issued under the 2017 Plan or with respect to which awards may be granted may not exceed 5,109,904 shares (including pursuant to incentive stock options), which may be either authorized and unissued shares of our common stock or shares of common stock held in or acquired for our treasury. The number of shares authorized under the 2017 Plan will be increased each January 1, commencing on January 1, 2018, by an amount equal to 4% of outstanding shares of stock as of the end of the immediately preceding fiscal year. Notwithstanding the foregoing, our board of directors may act prior to January 1 of a given year to provide that there will be no such January 1 increase in the number of shares of stock authorized under the 2017 Plan for such year or that the increase in the number of shares of stock authorized under the 2017 Plan for such year will be a lesser number than would otherwise occur pursuant to the preceding sentence. Notwithstanding the preceding sentences, in no event shall the number of shares available for issuance pursuant to incentive options over the term of the 2017 Plan exceed 4,018,538 shares of stock. In general, if awards under the 2017 Plan are for any reason cancelled, or expire or terminate unexercised, the number of shares covered by such awards will again be available for the grant of awards under the 2017 Plan.

Eligibility for Participation

Members of our board of directors, as well as employees of, and consultants and advisors to, us or any of our subsidiaries and affiliates are eligible to receive awards under the 2017 Plan. The selection of participants is within the sole discretion of the compensation committee.

Individual Limitations

The maximum number of shares of common stock that may be subject to options or stock appreciation rights or any combination thereof granted to any one person during any single calendar year shall be 1,200,000. The maximum number of shares of common stock that may be subject to all other awards granted to any one person during any single calendar year that are intended to be qualified performance-based awards shall be 1,200,000. The maximum value of awards denominated in cash granted to any one person other than a non-employee member of our board of directors during any single calendar year and that are intended to be qualified performance-based awards shall be $30,000,000. Each of the foregoing limitations shall be doubled with respect to awards granted to an individual during the first calendar year in which he or she commences employment. The maximum value of awards denominated in cash granted to any non-employee member of our board of directors during any single calendar year shall be $1,000,000.

Incentive Stock Options

Incentive stock options are options that are intended to qualify as incentive stock options under Section 422 of the Code, and will be granted pursuant to incentive stock option agreements. Only our employees or employees of our parent or subsidiary corporations, as contemplated by the Code, are eligible to receive incentive stock options. The compensation committee will determine the exercise price for an incentive stock option, which may not be less than 100% of the fair market value of the stock underlying the option on the date of grant. In addition, incentive options granted to employees who own, or are deemed to own, more than 10% of our voting stock, must have an exercise price not less than 110% of the fair market value of the stock underlying the option on the date of grant. No incentive stock option may be exercised on or after the tenth anniversary of the date of grant, or after the fifth anniversary of the date of grant for employees who own, or are deemed to own, more than 10% of our voting stock.

Nonstatutory Stock Options

Nonstatutory stock options are not intended to qualify as incentive stock options under Section 422 of the Code and will be granted pursuant to nonstatutory stock option agreements. The compensation committee will determine the exercise price which may not be less than 100% of the fair market value of the stock underlying the option on the date of grant and term of a nonstatutory stock option.

Stock Appreciation Rights

A stock appreciation right, or a SAR, entitles a participant to receive a payment equal in value to the difference between the fair market value of a share of stock on the date of exercise of the SAR over a specified exercise price of the SAR. SARs may be granted in tandem with a stock option, such that the recipient has the opportunity to exercise either the stock option or the SAR, but not both. The exercise price (above which any appreciation is measured) will not be less than 100% of the fair market value of the common stock on the date of grant of the SAR or, in the case of an SAR granted in tandem with a stock option, the exercise price will be the same as the exercise price of the related stock option. The compensation committee may settle a SAR amount in cash, in shares of our common stock, or a combination of cash and shares of our common stock as determined by the compensation committee at or after grant but subject to the terms of the applicable aware agreement. The terms, methods of exercise, and any other terms and conditions of any SAR will be determined by the compensation committee at the time of the grant of the award and will be reflected in the award agreement.

Restricted Stock and Restricted Stock Units

A restricted stock award or restricted stock unit award is the grant of shares of our common stock either currently (in the case of restricted stock) or at a future date (in the case of restricted stock units) at a price determined by the compensation committee (including zero), based on satisfaction of certain vesting conditions, including continuing employment or other service, or achievement of performance goals. During the vesting period, participants holding shares of restricted stock shall, except as otherwise provided in the Plan or an individual award agreement, have full voting and dividend rights with respect to such shares but any stock dividends or other distributions payable in shares of stock or other securities of ours will be subject to the same vesting conditions that apply to the shares of restricted stock in respect of which the dividend was made. The receipt of cash dividends may also be deferred or required to be invested in additional shares of restricted stock. Participants holding restricted stock units may be entitled to receive payments equivalent to any dividends declared with respect to the common stock referenced in the grant of the restricted stock units, but only following the close of the applicable restriction period and then only if the employment or other service and/or performance goals have been met. The restrictions will lapse in accordance with a schedule or other conditions determined by the compensation committee. The compensation committee may settle restricted stock units in cash, in shares of our common stock, or a combination of cash and shares of our common stock as determined by the compensation committee at or after grant but subject to the terms of the applicable award agreement.

Performance Units

A performance unit award is a contingent right to receive the value of a specified number of shares of our common stock over an initial value for such number of shares (which may be zero) established by the compensation committee at the time of grant if certain performance goals or other business objectives are met with the specified performance period. The value of performance units will depend on the degree to which the specified performance goals are achieved. The compensation committee may, in its discretion, pay earned performance units in cash, in shares of our common stock, or a combination of both cash and shares of our common stock as determined by the compensation committee at or after grant but subject to the terms of the applicable award agreement.

The compensation committee has discretion to select the length of any applicable restriction or performance period, the kind and/or level of the applicable performance goal and whether the performance goal is to apply to us, to one of our subsidiaries or any division or business unit or to the recipient.

Stock Grants

A stock grant is an award of shares of common stock without restriction. Stock grants may only be made in limited circumstances, such as in lieu of other earned compensation or as an inducement to employment. Stock grants are made without any forfeiture conditions.

Qualified Performance-Based Awards

Qualified performance-based awards are earned based on the achievement of certain performance criteria intended to satisfy Section 162(m) of the Code. Section 162(m) of the Code limits our federal income tax deduction for compensation to certain of our executive officers to $1.0 million dollars, but excludes from that limit "performance-based compensation." Any form of award permitted under the 2017 Plan other than a stock grant may be granted as a qualified performance-based award, but, in the case of awards other than stock options and SARs, will be subject to satisfaction of pre-established, objective performance goals. Qualified performance-based awards include any of the foregoing awards that are granted subject to vesting and/or payment based on the attainment of specified performance goals. Performance criteria upon which performance goals are established by the plan administrator may include but are not limited to: (i) net earnings (either before or after one or more of (A) interest, (B) taxes, (C) depreciation and (D) amortization); (ii) gross or net sales or revenue; (iii) net income (either before or after taxes); (iv) adjusted net income; (v) operating earnings or profit; (vi) cash flow (including, but not limited to, operating cash flow and free cash flow); (vii) return on assets; (viii) return on capital; (ix) return on stockholders' equity; (x) total stockholder return; (xi) return on sales; (xii) gross or net profit or operating margin; (xiii) costs; (xiv) expenses; (xv) working capital; (xvi) earnings per share; (xvii) adjusted earnings per share; (xviii) price per share; (xix) regulatory body approval for commercialization of a product; (xx) implementation, completion or attainment of objectives relating to research, development, regulatory, commercial or strategic milestones or developments; (xxi) market share; (xxii) economic value; (xxiii) revenue; (xxiv) revenue growth; and (xxv) operational and organizational metrics.

Transferability

Awards, other than stock grants, granted under the 2017 Plan are generally nontransferable (other than by will or the laws of descent and distribution), except that the compensation committee may, at the time of grant or thereafter, provide for the transferability of nonstatutory stock options or restricted stock to certain family members and/or certain trusts, foundations or other entities owned or controlled by such family members.

Adjustment for Corporate Actions

In the event of any change in the outstanding shares of common stock as a result of a reorganization, recapitalization, reclassification, stock dividend, stock split, reverse stock split or other similar distribution with respect to the shares of common stock, an equitable adjustment will be made in (i) the maximum numbers and kinds of shares subject to the 2017 Plan, (ii) the numbers and kinds of shares or other securities subject to then outstanding awards, (iii) the exercise price for each share or unit of any other securities subject to then outstanding stock options or SARs (without change in the aggregate purchase price as to which such stock options or SARs remain exercisable), and (iv) the repurchase price of each share of restricted stock then subject to a risk of forfeiture in the form of a company repurchase right. Any such adjustment in awards will be determined and made by the compensation committee in its sole discretion.

Transactions

In the event of a transaction, including (i) any merger or consolidation of our company with or into another entity as a result of which our stock is converted into or exchanged for the right to receive cash, securities or other property or is cancelled, (ii) any sale or exchange of all or substantially all of our common stock for cash, securities, or other property, (iii) any sale, transfer or other disposition of all or substantially all of our assets to one or more other persons in a single transaction or series of related transactions, or (iv) any liquidation or dissolution of our company, the compensation committee may, (1) provide that awards will be assumed, or substantially equivalent rights shall be provided in substitution therefor by the acquiring or succeeding entity (or an affiliate thereof), (2) upon written notice to the recipient, provide that the recipient's unexercised outstanding stock options and SARs will terminate immediately prior to the consummation of such transaction unless exercised within a specified period following the date of such written notice, (3) provide that all or any unvested restricted stock or restricted stock unit awards will terminate immediately prior to the consummation of such transaction, (4) provide that all or any outstanding stock options and SARs shall become exercisable in whole or in part prior to or upon the transaction, (5) provide that the vesting of all or any unrestricted stock or restricted stock unit awards shall accelerate and any restrictions applicable to such awards shall lapse prior to or upon such transaction, (6) provide for cash payments, net of applicable tax withholdings, to be made to the recipients, (7) provide that, in connection with our liquidation or dissolution, awards other than awards of restricted stock or stock grants shall convert into the right to receive liquidation proceeds net of the exercise price of the awards and any applicable tax withholdings, or (8) any combination of the foregoing. With respect to outstanding awards other than stock options or SARs, that are not terminated prior to or upon the transaction, upon the occurrence of a transaction other than our liquidation or dissolution which is not part of another form of transaction, our repurchase and other rights under each such award will transfer to our successor and inure to the benefit of our successor, and shall, unless the compensation committee determines otherwise, apply to the cash, securities or other property which the stock was converted into or exchanged for pursuant to such transaction in the same manner and to the same extent as they applied to the award. In taking any of the actions described in the event of a transaction, the compensation committee is not obligated to treat all awards, all awards held by a participant or all awards of the same type identically.

Change of Control

Except as otherwise provided in the 2017 Plan or in the applicable award agreement, in the event of a change of control, to the extent that the surviving entity declines to continue, convert, assume or replace outstanding awards, then all such awards shall become fully vested and exercisable and any restrictions applicable to any such awards shall lapse in connection with the transaction.

A change of control is defined as the occurrence of any of the following: (1) a transaction, as described above, unless securities possessing more than 50% of the total combined voting power of the resulting entity or acquiror's outstanding securities (or the securities of any parent thereof) are held by a person or persons who held securities possessing more than 50% of the total combined voting power of our outstanding securities immediately prior to the transaction; (2) any person or group of persons, excluding our company and certain other related entities or any of its affiliates, directly or indirectly acquires, including but not limited to by means of a merger or consolidation, beneficial ownership of securities possessing more than 50% of the total combined voting power of our outstanding securities, unless pursuant to a tender or exchange offer made directly to our stockholders that our board of directors recommends such stockholders accept; or (3) over a period of no more than 36 consecutive months there is a change in the composition of our board such that a majority of the board members ceases to be composed of individuals who either (i) have been board members continuously since the beginning of that period, or (ii) have been elected or nominated for election as board members during such period by at least a majority of the remaining board members who have been board members continuously since the beginning of that period; or (4) a majority of the board of directors votes in favor of a decision that a change of control has occurred.

Amendment and Termination

Our board of directors may at any time amend any or all of the provisions of the 2017 Plan, or suspend or terminate it entirely, retroactively or otherwise. However, except as set forth in the Plan, we must obtain stockholder approval to increase the number of shares available under the Plan, or to change the description of persons eligible for awards, or as otherwise required by law or applicable stock exchange rules. Unless otherwise required by law or specifically provided in the Plan, the rights of a participant under awards granted prior to any amendment, suspension or termination may not be adversely affected without the consent of the participant. Unless the 2017 Plan is earlier terminated by our board of directors, the Plan terminates immediately prior to the tenth anniversary of the effective date.

Allocation of Awards; Plan Benefits.

It is not presently possible to determine the dollar value of award payments that may be made or the number of options, shares of restricted stock, restricted stock units, or other awards that may be granted under the 2017 Plan in the future, or the individuals who may be selected to receive such awards because awards under the 2017 Plan are granted at the discretion of the compensation committee.

2015 Equity Incentive Plan

The 2015 Equity Incentive Plan, or the 2015 Plan was adopted on August 3, 2015, and was amended on January 5, 2017 to increase the number of shares issuable under the 2015 Plan. The following summary of the 2015 Plan does not purport to be complete and is qualified by reference to the full text of the 2015 Plan. The 2015 Plan was terminated and no further awards are granted under the 2015 Plan. All awards outstanding under the 2015 Plan were transferred to the 2017 Plan and are treated as outstanding under the 2017 Plan. However, each such transferred award continues to be governed by its existing terms.

The 2015 Plan provides for the grant of incentive stock options and nonstatutory stock options, restricted stock awards and stock grants, which we collectively refer to as "awards" in connection with the 2017 Plan. Our directors, officers and other employees, as well as consultants were eligible to receive grants under the 2015 Plan. The purpose of the 2015 Plan was to encourage ownership of our common stock by employees, consultants, officers and directors and to provide additional incentive to them to promote the success of our business.

Administration

Under its terms, the 2015 Plan is administered by the compensation committee of our board of directors which is made up of independent outside non-employee directors for purposes of applicable securities and tax laws. The board of directors itself may also exercise any of the powers and responsibilities under the 2015 Plan. The compensation committee may delegate to an executive officer or officers the authority to grant awards under the 2015 Plan subject to applicable law and to guidelines specified by the compensation committee. Subject to the terms of the 2015 Plan, the compensation committee will select the recipients of awards and determine, among other things, the:

- recipient of an award;
- form of award and the exercise or purchase price and method of payment for each such award;
- vesting period for awards, risks of forfeiture and any potential acceleration of vesting or lapses in risks of forfeiture; and
- duration of awards.

All determinations made in good faith by the compensation committee with respect to the 2015 Plan and the terms and conditions of or operation of any award are final and binding on all participants, beneficiaries, heirs, assigns or other persons holding or claiming rights under the 2015 Plan or any award.

Available Shares

The aggregate number of shares of our common stock which may be issued under the 2015 Plan or with respect to which awards may be granted may not exceed 2,317,339 shares (including pursuant to incentive stock options), which may be either authorized and unissued shares of our common stock or shares of common stock held in or acquired for our treasury. In general, if awards under the 2015 Plan are for any reason cancelled, or expire or terminate unexercised, the number of shares covered by such awards will again be available for the grant of awards under the 2015 Plan.

Eligibility for Participation

Members of our board of directors, as well as employees of, and consultants to, us or any of our subsidiaries and affiliates are eligible to receive awards under the 2015 Plan. The selection of participants is within the sole discretion of the compensation committee.

Stock Options

The 2015 Plan provides for the grant of nonstatutory stock options and incentive stock options. Incentive stock options may only be granted to employees. The exercise price of an incentive stock option must be at least 100% of the fair market value of the common stock on the grant date, or 110% for employees who own or are deemed to own more than 10% of our voting stock. No incentive stock option may be exercised on or after the tenth anniversary or the grant date or after the fifth anniversary of the grant date for employees who own or are deemed to own more than 10% of our voting stock. Stock options generally are not transferable except by will or the laws of descent and distribution

Restricted Stock

A restricted stock award is the grant of shares of our common stock at a price determined by the compensation committee (including zero), based on satisfaction of certain vesting conditions, including continuing employment or other service, or achievement of performance goals. During the vesting period, participants holding shares of restricted stock shall, except as otherwise provided in the 2015 Plan or an individual award agreement, have full voting rights with respect to such shares. In general, restricted stock may not be sold, transferred, pledged, assigned or otherwise alienated or hypothecated until the restrictions have lapsed or are removed. The restrictions lapse in accordance with a schedule or other conditions determined by the compensation committee.

Stock Grants

A stock grant is an award of shares of common stock without restriction for such consideration, in cash, other property or services or any combination thereof, as is determined by the committee. Stock grants may be awarded in such circumstances as the committee deems appropriate, including in recognition of significant contributions to our success or in lieu of compensation already due.

Adjustment for Corporate Actions

In the event of any change in the outstanding shares of common stock as a result of a reorganization, recapitalization, reclassification, stock dividend, stock split, reverse stock split or other similar distribution with respect to the shares of common stock, an appropriate and proportionate adjustment will be made in (i) the maximum numbers and kinds of shares subject to the 2015 Plan, (ii) the numbers and kinds of shares or other securities subject to then outstanding awards, (iii) the exercise price for each share subject to then outstanding stock options, and (iv) the repurchase price of each share of restricted stock then subject to a risk of forfeiture in the form of a company repurchase right. Any such adjustment in awards will be determined and made by the compensation committee in its sole discretion.

Change of Control

Except as otherwise provided in the 2015 Plan or in the applicable award agreement, in the event of a change of control, the committee has the discretion to determine the treatment of each outstanding award and may provide that the awards will be assumed or substituted, that the awards will terminate or accelerate in full immediately prior to the change in control, or that awards will terminate in exchange for cash or other property.

2017 Employee Stock Purchase Plan

Our board of directors have adopted and our stockholders have approved the 2017 employee stock purchase plan, or the ESPP, which will become effective immediately prior to the completion of this offering. The following summary of the material terms of the ESPP does not purport to be complete and is qualified by reference to the full text of the ESPP, which is filed as an exhibit to our registration statement of which this prospectus is a part.

The ESPP provides an incentive to, and encourages stock ownership by, all of our eligible employees and those of our participating subsidiaries so that they may share in our growth by acquiring or increasing their share ownership in us. It is intended that the ESPP constitute an "employee stock purchase plan" within the meaning of Section 423 of the Code. Under the ESPP, eligible employees may purchase shares of our common stock at a discount through payroll deductions.

Administration

The ESPP is administered by the compensation committee of our board of directors. The board of directors itself may exercise any of the powers and responsibilities under the ESPP. The compensation committee may delegate its duties in order to facilitate the purchase and transfer of shares of our common stock and for the day-to-day administration of the ESPP. The compensation committee, has the discretion, subject to the provisions of the ESPP, to make or to select the manner of making all determinations with respect to options granted under the ESPP. Further, the compensation committee has complete authority to interpret the ESPP, to prescribe, amend and rescind rules and regulations relating to it, and to make all other determinations necessary or advisable for the administration of the ESPP. All decisions, determinations and interpretations made in good faith by the compensation committee with respect to the ESPP are final and binding on all persons having or claiming any interest in the ESPP or any option granted under the ESPP.

Shares Subject to the Plan

The shares issued or to be issued under the ESPP are authorized but unissued shares of our common stock or are shares held by us in our treasury. Subject to the following sentence, the ESPP authorizes the issuance of up to 272,841 shares of common stock. The number of shares authorized under the ESPP will be increased each January 1, commencing on January 1, 2019 and ending on (and including) January 1, 2027, by an amount equal to the lesser of 1% of outstanding shares as of the end of the immediately preceding fiscal year and 655,666. Notwithstanding the foregoing, our board of directors may act prior to January 1 of a given year to provide that there will be no such January 1 increase in the number of shares authorized under the ESPP for such year, or that the increase in the number of shares authorized under the ESPP for such year will be a lesser number than would otherwise occur pursuant to the preceding sentence.

Terms of Participation

The ESPP will be implemented through a series of purchase periods called "plan periods." The initial plan period shall commence on September 1, 2018 and will continue for six months. After the initial plan period, there will be two consecutive six-month plan periods, during each twelve-month period thereafter, with the first six-month Plan Period beginning on March 1 and ending on the immediately following August 31, and the second six-month Plan Period beginning on September 1 and ending on the immediately following February 28 unless otherwise determined by the compensation committee. Notwithstanding the foregoing, the Chief Executive Officer and/or Chief Financial Officer of the Company shall have the authority, in their sole discretion, to select different dates for the start date of the initial plan period and the subsequent plan periods. An eligible employee will be granted an option at the beginning of the plan period, and can accumulate money to pay the exercise price for the option by electing to have payroll deductions taken from each payroll during a plan period of an amount, in whole percentages, between 1% and 15% of his or her compensation, but will not exceed $25,000 on an annual basis. At the end of each plan period, unless the participating employee has withdrawn from the ESPP, the option will be exercised by applying the employee's accumulated payroll deductions to the purchase of shares of our common stock. The exercise price paid by the employee will be the lower of 85% of the fair market value of our common stock at (i) the commencement of the plan period and (ii) the end of the plan period.

Withdrawal

An employee may withdraw from participation in an offering up to two weeks prior to the plan period termination date and permanently draw out the balance accumulated in his or her account. In such case, the employee's option for the plan period he or she is withdrawing from will be automatically terminated. A participant's withdrawal from a plan period will not have any effect upon his or her eligibility to participate in a succeeding plan period or in any similar plan which we may adopt. If a participant's employment ends prior to a plan period termination date for any reason, including retirement or death, the contributions credited to his or her account will be returned to him or her or, in the case of his or her death, to his or her designated beneficiaries, and his or her option will be automatically terminated.

Eligibility

Our employees and those of a participating subsidiary are eligible to participate in the ESPP if we customarily employ them for at least 20 hours per week and more than five months per year, provided that the compensation committee may waive one or both requirements prior to the start of a plan period. However, no employee shall be granted an option under the ESPP if, immediately after the grant, the employee would own stock, including any outstanding options to purchase stock, equaling 5% or more of the total voting power or value of all classes of our stock. In addition, the ESPP provides that no employee may be granted an option if the option would permit the employee to purchase stock under all of our employee stock purchase plans in an amount that exceeds $25,000 of the fair market value of such stock, determined as of the date(s) of grant, for each calendar year in which the option is outstanding.

Adjustment for Corporate Actions

In the event of any change in the outstanding shares of common stock as a result of a reorganization, recapitalization, reclassification, stock dividend, stock split, reverse stock split, or other similar distribution with respect to the shares of common stock, an appropriate and proportionate adjustment will be made in (i) the maximum numbers and kinds of shares subject to the ESPP, (ii) the numbers and kinds of shares or other securities subject to the then outstanding options, and (iii) the exercise price for each share or other unit of any other securities subject to then outstanding options.

Corporate Transactions

In the event of our dissolution or liquidation, the plan period then in progress will terminate unless otherwise provided by the compensation committee. In the event of another significant corporate transaction such as a merger or consolidation of us with and into another person or entity or the sale or transfer of all or substantially all of our assets, each right to purchase stock under the ESPP may be assumed, or an equivalent right substituted by, the successor corporation or a parent or subsidiary of the successor corporation. In the event that the successor corporation refuses to assume each purchase right or to substitute an equivalent right, any ongoing offering period will be shortened so that employees' rights to purchase stock under the ESPP are exercised prior to the transaction, unless the employee has withdrawn.

Amendment and Termination

Our board of directors has the power to amend or terminate the ESPP and to change or terminate plan periods as long as any such action does not adversely affect any outstanding rights to purchase stock; provided, however, that the board of directors may amend or terminate the ESPP or a plan period even if it would adversely affect outstanding options in order to avoid our incurring adverse accounting charges or if the board of directors determines that termination of the ESPP and/or plan period is in our best interest and the best interest of our stockholders. The ESPP will continue in effect until the tenth anniversary of the closing of the offering described in this prospectus, unless earlier terminated by the board of directors.

Amount of Benefits

The dollar value of benefits that will be received by any employee or group of employees in the ESPP is not determinable due to the voluntary nature of the ESPP and the variables involved in the calculation of any such benefits (including our stock price).

401(k) Plan

We maintain a tax qualified retirement plan that provides eligible U.S. employees with an opportunity to save for retirement on a tax advantaged basis. Eligible employees are able to defer eligible compensation up to certain Code limits, which are updated annually. We have the ability to make matching and discretionary contributions to the 401(k) plan but have not done so to date. Employee contributions are allocated to each participant's individual account and are then invested in selected investment alternatives according to the participants' directions. Employees are immediately and fully vested in their own contributions. The 401(k) plan is intended to be qualified under Section 401(a) of the Code, with the related trust intended to be tax exempt under Section 501(a) of the Code. As a tax qualified retirement plan, contributions to the 401(k) plan are deductible by us when made, and contributions and earnings on those amounts are not taxable to the employees until withdrawn or distributed from the 401(k) plan.

Non-Employee Director Compensation

Under our director compensation program, we pay our non-employee directors retainers in cash. We do not pay any compensation to our President and Chief Executive Officer in connection with his service on our Board and, consequently, he is not included in the table. The compensation that we pay to our President and Chief Executive Officer is discussed in the "Executive Compensation" section of this prospectus. Each non-employee director receives an annual retainer fee of $35,000 paid in arrears. In addition, non-employee directors receive the following, as applicable:

Non-Employee Director	Annual Fee
Lead Director	$ 25,000
Non-Executive Chair	$ 30,000
Chairman of the Audit Committee	$ 15,000
Member of the Audit Committee (other than chairman)	$ 7,500
Chairman of the Compensation Committee	$ 10,000
Member of the Compensation Committee (other than chairman)	$ 5,000
Chairman of the Governance and Nominating committee	$ 8,000
Member of the Governance and Nominating committee (other than chairman)	$ 4,000

We also reimburse our non-employee directors for reasonable travel and out-of-pocket expenses incurred in connection with attending Board and committee meetings.

Under the non-employee director compensation policy, each individual who is initially appointed or elected to the Board is also eligible to receive an option to purchase up to 20,000 shares of our common stock under our 2017 Equity Incentive Plan, or the Plan, on the date he or she first becomes a nonemployee director. These option grants vest annually over a three-year period from the date of grant, subject to continued service as a non-employee director through that vesting date. In addition, on the date of the annual meeting of stockholders, each continuing non-employee director who has served on the Board for a minimum of six months is eligible to receive an option grant to purchase 10,000 shares of our common stock, which will vest in full upon the earlier of the first anniversary of the date of grant or the date of the next annual meeting of stockholders. The exercise price for each of these option grants will be equal to the fair market value of our common stock on the date of grant. These new director grants and annual grants will be subject to approval by our Board at the time of grant.

This policy is intended to provide a total compensation package that enables us to attract and retain qualified and experienced individuals to serve as directors and to align our directors' interests with those of our stockholders.

Our current director compensation arrangements have been in effect since the time of our initial public offering in October 2017. Prior to that time, we did not have a formal non-employee director compensation policy. We reimbursed our non-employee directors for reasonable travel and out-of-pocket expenses incurred in connection with attending board of director and committee meetings.

The following table sets forth information regarding compensation earned by our non-employee directors during fiscal year 2017.

Name	Fees earned in cash ($)(1)	Option Awards ($)(2)(3)	Total ($)
Neil Exter	$ 11,250	—	$ 11,250
Todd Foley	$ 10,000	—	$ 10,000
Christophe R. Jean	$ 10,625	—	$ 10,625
Ed Mathers	$ 9,750	—	$ 9,750
David W. J. McGirr	$ 28,500	$ 80,000	$ 108,500
David P. Meeker	$ 27,625	$ 240,000	$ 267,625
Jonathan T. Silverstein, J.D.(4)	—	—	—

(1) Amounts represent annual cash compensation earned for services rendered by each member of the Board.
(2) The options granted to our Board during fiscal year 2017 vest annually over 3 years. These grants have a weighted average exercise price of $6.05 per option.
(3) Amounts shown reflect the grant date fair value of options awarded during fiscal year 2017 determined in accordance with the Financial Accounting Standards Board, Accounting Standards Codification Topic 718, *Compensation—Stock Compensation*. These amounts exclude the value of estimated forfeitures.
(4) Mr. Silverstein resigned from the Board in October 2017 concurrently with our initial public offering.

The following table sets forth, as of December 31, 2017, the aggregate number of exercisable and unexercisable option awards outstanding held by our non-employee directors at that time.

	Option Awards	
Name	Exercisable	Unexercisable
Neil Exter	—	—
Todd Foley	—	—
Christophe R. Jean	—	—
Ed Mathers	—	—
David W. J. McGirr	43,621	43,620
David P. Meeker	21,811	87,240
Jonathan T. Silverstein, J.D.(1)	—	—

(1) Mr. Silverstein resigned from the Board in October 2017 concurrently with our initial public offering.

Limitation on Liability and Indemnification Matters

Section 145 of the Delaware General Corporation Law authorizes a corporation's board of directors to grant, and authorizes a court to award, indemnity to officers, directors and other corporate agents.

As permitted by Delaware law, our amended and restated certificate of incorporation provides that, to the fullest extent permitted by Delaware law, no director will be personally liable to us or our stockholders for monetary damages for breach of fiduciary duty as a director. Pursuant to Delaware law, such protection would be not available for liability:

- for any breach of a duty of loyalty to us or our stockholders;
- for acts or omissions not in good faith or that involve intentional misconduct or a knowing violation of law;
- for any transaction from which the director derived an improper benefit; or

- for an act or omission for which the liability of a director is expressly provided by an applicable statute, including unlawful payments of dividends or unlawful stock repurchases or redemptions as provided in Section 174 of the Delaware General Corporation Law.

Our amended and restated certificate of incorporation also provides that if Delaware law is amended after the approval by our stockholders of the amended and restated certificate of incorporation to authorize corporate action further eliminating or limiting the personal liability of directors, then the liability of our directors will be eliminated or limited to the fullest extent permitted by Delaware law.

Our amended and restated bylaws further provide that we must indemnify our directors and officers to the fullest extent permitted by Delaware law. Our amended and restated bylaws also authorize us to indemnify any of our employees or agents and permit us to secure insurance on behalf of any officer, director, employee or agent for any liability arising out of his or her action in that capacity, whether or not Delaware law would otherwise permit indemnification.

In addition, our amended and restated bylaws provide that we are required to advance expenses to our directors and officers as incurred in connection with legal proceedings against them for which they may be indemnified and that the rights conferred in the amended and restated bylaws are not exclusive.

We have entered into indemnification agreements with each of our directors and executive officers. These agreements, among other things, require us to indemnify each director and officer to the fullest extent permitted by Delaware law, the amended and restated certificate of incorporation and amended and restated bylaws, for expenses such as, among other things, attorneys' fees, judgments, fines and settlement amounts incurred by the director or executive officer in any action or proceeding, including any action by or in our right, arising out of the person's services as our director or executive officer or as the director or executive officer of any subsidiary of ours or any other company or enterprise to which the person provides services at our request. We maintain directors' and officers' liability insurance.

The SEC has taken the position that personal liability of directors for violation of the federal securities laws cannot be limited and that indemnification by us for any such violation is unenforceable. The limitation of liability and indemnification provisions in our amended and restated certificate of incorporation and amended and restated bylaws may discourage stockholders from bringing a lawsuit against our directors and officers for breach of their fiduciary duty. They may also reduce the likelihood of derivative litigation against our directors and officers, even though an action, if successful, might benefit us and other stockholders. Further, a stockholder's investment may be adversely affected to the extent that we pay the costs of settlement and damage awards against directors and officers as required by these indemnification provisions.

Rule 10b5-1 Sales Plans

Our directors and executive officers may adopt written plans, known as Rule 10b5-1 plans, pursuant to which, if adopted, they would contract with a broker to buy or sell shares of our common stock on a periodic basis. Under a Rule 10b5-1 plan, a broker executes trades pursuant to parameters established by the director or officer when entering into the plan, without further direction from them. The director or officer may amend a Rule 10b5-1 plan in some circumstances and may terminate a plan at any time. Our directors and executive officers also may buy or sell additional shares outside of a Rule 10b5-1 plan when they are not in possession of material nonpublic information subject to compliance with the terms of our insider trading policy. Prior to 90 days after the date of this offering (subject to early termination), the sale of any shares under such plan would be subject to the lock-up agreement that the director or officer has entered into with the underwriters.

TRANSACTIONS WITH RELATED PERSONS

We describe below transactions and series of similar transactions, during our last three fiscal years, to which we were a party or will be a party, in which:

- the amounts involved exceeded or will exceed $120,000; and
- any of the directors, executive officers or holders of more than 5% of our voting equity, or any member of the immediate family of the foregoing persons, had or will have a direct or indirect material interest.

Compensation arrangements for our directors and named executive officers are described elsewhere in this prospectus.

Series A Preferred Stock Financing

In January 2017 and August 2017, pursuant to the series A preferred stock purchase agreement we issued an aggregate of 40,949,999 shares of series A preferred stock, par value $0.001 per share, at a purchase price of $1.00 per share, resulting in aggregate gross proceeds of $40.9 million to us.

Holders of our series A preferred stock are entitled to certain registration rights with respect to the resale of such shares under the Securities Act, pursuant to the investors' rights agreement entered into between us and certain of our stockholders. See "*Description of Capital Stock—Registration Rights.*"

The following table summarizes the participation in the series A preferred stock financing by our directors, executive officers, holders of more than 5% of our voting securities, or any member of the immediate family of the foregoing persons. For further information on the ownership of securities of our directors, executive officers and holders of more than 5% of our voting securities, see "*Principal Stockholders.*"

Name	Shares of Series A Preferred Stock	Date(s) Purchased
New Enterprise Associates 13, L.P.	5,067,162	January 6, 2017
Third Rock Ventures, L.P.	4,624,751	January 6, 2017
MPM BioVentures V, L.P. and MPM Asset Management Investors BV5 LLC	3,015,916	January 6, 2017
OrbiMed Private Investments V, LP	2,924,766	January 6, 2017
Pfizer Inc.	1,611,852	January 6, 2017
667 L.P. and Baker Brothers Life Sciences, L.P.	1,337,036	January 6, 2017
David P. Meeker	250,000	January 6, 2017
Keith M. Gottesdiener, M.D.	125,000	January 6, 2017
Bart Henderson	100,000	January 6, 2017
New Enterprise Associates 13, L.P.	5,067,162	August 18, 2017
Third Rock Ventures, L.P.	4,624,751	August 18, 2017
MPM BioVentures V, L.P. and MPM Asset Management Investors BV5 LLC	3,015,915	August 18, 2017
OrbiMed Private Investments V, LP	2,924,765	August 18, 2017
Pfizer Inc.	1,611,852	August 18, 2017
667 L.P. and Baker Brothers Life Sciences, L.P.	1,337,035	August 18, 2017
David P. Meeker	250,000	August 18, 2017
Keith M. Gottesdiener, M.D.	125,000	August 18, 2017
Bart Henderson	100,000	August 18, 2017

Indemnification Agreements

We currently have indemnification agreements with each of our directors and executive officers. These agreements, among other things, require us to indemnify each director and officer to the fullest extent permitted by Delaware law, our amended and restated certificate of incorporation and amended and restated bylaws, for expenses such as, among other things, attorneys' fees, judgments, fines, and settlement amounts incurred by the director or executive officer in any action or proceeding, including any action by or in our right, arising out of the person's services as our director or executive officer or as the director or executive officer of any subsidiary of ours or any other company or enterprise to which the person provides services at our request. We maintain directors' and officers' liability insurance. See "*Executive and Director Compensation—Limitation on Liability and Indemnification Matters.*"

Employment and Board Arrangements

Our executive officers have employment letters with us for their services. For information about the employment letters with our named executive officers, refer to "*Executive and Director Compensation—Agreements with our Executive Officers*."

Consulting Agreement with Mr. Henderson

Mr. Henderson resigned from employment with us as President in June 2017 and thereafter entered into a consulting agreement with us. Under the terms of Mr. Henderson's consulting agreement, he was entitled to a consulting fee on an hourly basis, subject to adjustment by us. In consideration of Mr. Henderson's prior service to us as a founder and former officer and employee, under the terms of Mr. Henderson's consulting agreement with us, Mr. Henderson continued to vest in any unvested equity awards held by him, through and including December 31, 2017, with a right to exercise any vested equity through and including October 1, 2018.

Related Party Transactions Policy

Our Board has adopted a policy that our executive officers, directors, nominees for election as a director, beneficial owners of more than 5% of any class of our common stock and any members of the immediate family of any of the foregoing persons are not permitted to enter into a related person transaction with us without the prior review and approval of our Governance and Nominating committee. Any request for us to enter into a transaction with an executive officer, director, nominee for election as a director, beneficial owner of more than 5% of any class of our common stock or any member of the immediate family of any of the foregoing persons in which the amount involved exceeds $120,000 and such person would have a direct or indirect material interest must first be presented to our Governance and Nominating committee for review, consideration and approval. In approving or rejecting any such proposal, our Governance and Nominating committee is to consider the material facts of the transaction, including, but not limited to, whether the transaction is on terms no less favorable than terms generally available to an unaffiliated third party under the same or similar circumstances and the extent of the related person's interest in the transaction. We did not have a formal review and approval policy for related party transactions at the time of any of the transactions described above. However, the transactions described under "*Transactions with Related Persons"* were entered into after presentation, consideration and approval by our Board.

PRINCIPAL STOCKHOLDERS

The following table sets forth certain information as of May 31, 2018 (unless otherwise specified), with respect to the beneficial ownership of our common stock by each person who is known to own beneficially more than 5% of the outstanding shares of common stock, each person currently serving as a director, each nominee for director, each named executive officer (as set forth in the Summary Compensation Table below), and all directors and executive officers as a group.

Shares of common stock subject to options or other rights to purchase which are now exercisable or are exercisable within 60 days after May 31, 2018, are to be considered outstanding for purposes of computing the number of shares beneficially owned and the percentage ownership of the persons holding these options or other rights, but are not to be considered outstanding for the purpose of computing the number of shares beneficially owned or the percentage ownership of any other person. As of May 31, 2018, there were 27,530,184 shares of common stock outstanding. Unless otherwise indicated, the address for each beneficial owner is c/o Rhythm Pharmaceuticals, Inc., 500 Boylston Street, 11th Floor, Boston, MA 02116.

Beneficial ownership is determined according to the rules of the SEC and generally means that a person has beneficial ownership of a security if he, she or it possesses sole or shared voting or investment power of that security, and of convertible securities that are currently exercisable or exercisable within 60 days after May 31, 2018. Shares of our common stock issuable pursuant to options or warrants, if any, are deemed outstanding for computing the percentage of the person holding such options or warrants and the percentage of any group of which the person is a member but are not deemed outstanding for computing the percentage of any other person.

Our calculation of the percentage of beneficial ownership after this offering is based on 32,131,411 shares of common stock outstanding immediately after the closing of this offering (assuming no exercise of the underwriters' option to purchase additional shares of our common stock). Except as indicated by the footnotes below, we believe, based on the information furnished to us, that the persons named in the table below have sole voting and investment power with respect to all shares of common stock shown that they beneficially own, subject to community property laws where applicable. The information does not necessarily indicate beneficial ownership for any other purpose, including for purposes of Section 13(d) and 13(g) of the Securities Act. If any shares are purchased by our existing principal stockholders, directors or their affiliated entities, the number and percentage of shares of our common stock beneficially owned by them after this offering will differ from those set forth in the following table.

Except as otherwise noted below, the address for persons listed in the table is c/o Rhythm Pharmaceuticals, Inc., 500 Boylston Street, Eleventh Floor, Boston, MA 02116.

Name and Address of Beneficial Owner	Prior to the Offering: Number of shares of common stock	Prior to the Offering: Percent of class	After the Offering: Number of shares of common stock	After the Offering: Percent of class
5% Stockholders:				
New Enterprise Associates 13, L.P. and NEA Ventures 2009 Limited Partnership[(1)] 2855 Sand Hill Road Menlo Park, CA 94025	4,912,306	17.84%	4,912,306	15.29%
Third Rock Ventures, L.P.[(2)] 29 Newbury Street Boston, MA 02116	3,981,437	14.46%	3,981,437	12.39%
MPM BioVentures V, L.P. and MPM Asset Management Investors BV5 LLC[(3)] 450 Kendall Street Cambridge, MA 02142	2,696,392	9.79%	2,696,392	8.39%
OrbiMed Private Investments V, LP[(4)] 601 Lexington Avenue, 54th Floor New York NY 10022-4629	2,375,000	8.63%	2,375,000	7.39%
667, L.P. and Baker Brothers Life Sciences, L.P.[(5)] 667 Madison avenue, 21st Floor New York, NY 10065	2,049,020	7.44%	2,049,020	6.38%
Pfizer Inc.[(6)] 235 East 42nd Street New York, NY 10017	1,427,639	5.19%	1,427,639	4.44%
Directors and Named Executive Officers:				
Keith M. Gottesdiener[(7)]	788,867	2.84%	788,867	2.44%
Hunter C. Smith[(8)]	3,812	*	3,812	*
Nithya Desikan[(9)]	78,784	*	78,784	*
Todd Foley	—	—	—	—
Ed Mathers	—	—	—	—
Neil Exter	—	—	—	—
Christophe R. Jean	—	—	—	—
David Meeker[(10)]	144,956	*	144,956	*
David McGirr[(11)]	50,891	*	50,891	*
All executive officers and directors as a group (11 persons)[(12)]	1,444,233	5.14%	1,444,233	4.42%

* Represents beneficial ownership of less than 1%.

(1) The shares held directly by NEA Ventures 2009, L.P., or NEA 2009, are indirectly held by Karen P. Welsh, the general partner of NEA 2009 and the shares held by New Enterprise Associates 13, L.P., or NEA 13, are indirectly held by NEA Partners 13, L.P., or Partners 13, which is the sole general partner of NEA 13; NEA 13 GP, LTD, or NEA 13 LTD, which is the sole general partner of Partners 13; and each of the individual directors of NEA 13 LTD. The individual Directors of NEA 13 LTD, or the NEA 13 Directors, are M. James Barrett, Peter J. Barris, Forest Baskett, Patrick J. Kerins, David M. Mott, Scott D. Sandell and Ravi Viswanathan. Karen P. Welsh holds voting and dispositive power with regard to the shares held by NEA 2009. NEA Partners 13, NEA 13 LTD, and the NEA 13 Directors share voting and dispositive power with regard to the shares owned directly by NEA 13. All indirect holders of the above referenced shares disclaim beneficial ownership of all applicable shares except to the extent of their actual pecuniary interest therein.

(2) Based solely on a Schedule 13G filed on February 13, 2018, each of Third Rock Ventures GP, LP, or TRV GP, the general partner of Third Rock Ventures, L.P., or TRV LP, and Third Rock Ventures GP, LLC, TRV LLC, the general partner of TRV GP, and Mark Levin, Kevin Starr and Robert Tepper, the managers of TRV LLC, may be deemed to share voting and investment power over the shares held by TRV LP. Each of the reporting persons disclaims beneficial ownership of such shares, except to the extent of their proportionate pecuniary interest therein, if any.

(3) Based solely on a Schedule 13D filed on October 24, 2017, MPM BioVentures V LLC is the Managing Member of MPM BioVentures V GP LLC, which is the General Partner of MPM BioVentures V, L.P. MPM BioVentures V LLC is the Manager of MPM Asset Management Investors BV5 LLC. Todd Foley, one of our directors, is a Member of MPM BioVentures V LLC

and shares the power to vote, hold and dispose of the shares held by MPM BioVentures V, L.P., and MPM Asset Management Investors BV5 LLC. Mr. Foley and each such other Member of MPM BioVentures V LLC disclaims beneficial ownership of the securities reported herein except to the extent of his respective pecuniary interest therein.

(4) Based solely on Amendment No. 1 to Schedule 13D filed on February 7, 2018, OrbiMed Capital GP V LLC, or GP V, is the sole general partner of OrbiMed Private Investments V, LP, or OPI V, and OrbiMed Advisors LLC, or Advisors, a registered adviser under the Investment Advisers Act of 1940, as amended, is the sole managing member of GP V. By virtue of such relationships, GP V and Advisors may be deemed to have voting and investment power with respect to the shares held by OPI V noted above and as a result may be deemed to have beneficial ownership over such shares. Advisors exercises this investment and voting power through a management committee comprised of Carl L. Gordon, Sven H. Borho and Jonathan T. Silverstein. Each of GP V, Advisors, Mr. Gordon, Mr. Borho, and Mr. Silverstein disclaims beneficial ownership of the shares held by OPI V, except to the extent of its or his pecuniary interest therein if any.

(5) Based solely on a Schedule 13G filed on February 13, 2018, Baker Bros. Advisors LP, or Baker Bros. Advisors, is the investment adviser to 667, L.P., or 667 LP, and Baker Brothers Life Sciences, L.P., or Baker Brothers Life Sciences, and, pursuant to amended and restated management agreements between Baker Bros. Advisors, 667 LP and Baker Brothers Life Sciences and the respective general partners of 667 LP and Baker Brother Life Sciences, Baker Bros. Advisors has complete and unlimited discretion and authority with respect to the investments and voting power over investments of 667 LP and Baker Brothers Life Sciences. Baker Bros. Advisors disclaims beneficial ownership of all shares held by 667 LP and Baker Brothers Life Sciences except to the extent of any pecuniary interest therein.

(6) As of May 31, 2018, the board of directors of Pfizer Inc. is comprised of the following individuals: Dennis A. Ausiello, Ronald E. Blaylock, Albert Bourla, W. Don Cornwell, Joseph J. Echevarria, Helen H. Hobbs, James M. Kilts, Dan R. Littman, Shantanu Narayen, Suzanne Nora Johnson, Ian C. Read, and James C. Smith. Pfizer Inc. is a publicly traded company.

(7) Consists of (i) 588,539 shares of common stock and (ii) includes 200,328 shares of common stock underlying options that are exercisable within 60 days of May 31, 2018.

(8) Includes 3,812 shares of common stock underlying options that are exercisable within 60 days of May 31, 2018.

(9) Includes of 73,087 shares of common stock underlying options that are exercisable within 60 days of May 31, 2018.

(10) Consists of (i) 101,335 shares of common stock and (ii) includes 43,621 shares of common stock underlying options that are exercisable within 60 days of May 31, 2018.

(11) Includes 50,891 shares of common stock underlying options that are exercisable within 60 days of May 31, 2018.

(12) Consists of (i) 886,112 shares of common stock and (ii) includes 558,121 shares of common stock underlying options that are exercisable within 60 days of May 31, 2018.

DESCRIPTION OF CAPITAL STOCK

The following is a description of certain provisions of our amended and restated certificate of incorporation and restated bylaws, both of which were adopted in connection with our initial public offering in October 2017, and certain provisions of our outstanding options and the Delaware General Corporation Law, or DGCL. The following description does not purport to be complete and is subject to, and qualified in its entirety by reference to, the forms of our amended and restated certificate of incorporation and restated bylaws, the forms of stock option agreements filed as exhibits to the registration statement, of which this prospectus forms a part, and the terms and provisions of the DGCL. For more complete information, you should carefully review the forms of our amended and restated certificate of incorporation and amended and restated bylaws and stock option agreements, which have been filed with the SEC as exhibits to our registration statement of which this prospectus forms a part and which may be obtained as described below under "Where You Can Find More Information."

Our authorized capital stock consists of 120,000,000 shares of common stock, par value $0.001 per share, our "common stock," and 10,000,000 shares of preferred stock, par value $0.001 per share, our "preferred stock."

As of March 31, 2018, there were 27,284,140 shares of our common stock outstanding, held by approximately 28 stockholders of record, and 2,427,629 shares of our common stock issuable upon the exercise of outstanding stock options.

Common Stock

Holders of shares of our common stock are entitled to one vote for each share held of record on all matters submitted to a vote of stockholders. The holders of a plurality of the shares of our common stock entitled to vote in any election of directors can elect all of the directors standing for election.

Holders of shares of our common stock are entitled to receive dividends when and if declared by our board of directors out of funds legally available therefor, subject to any statutory or contractual restrictions on the payment of dividends and to any restrictions on the payment of dividends imposed by the terms of any outstanding preferred stock.

Upon our dissolution or liquidation or the sale of all or substantially all of our assets, after payment in full of all amounts required to be paid to creditors and to the holders of preferred stock having liquidation preferences, if any, the holders of shares of our common stock will be entitled to receive pro rata our remaining assets available for distribution.

Holders of shares of our common stock do not have preemptive, subscription, redemption or conversion rights.

Preferred Stock

Our amended and restated certificate of incorporation authorizes our board of directors to establish one or more series of preferred stock (including convertible preferred stock). Unless required by law or by any stock exchange, the authorized shares of preferred stock will be available for issuance without further action by our stockholders. Our board of directors is able to determine, with respect to any series of preferred stock, the terms and rights of that series, including:

- the designation of the series;
- the number of shares of the series, which our board may, except where otherwise provided in the preferred stock designation, increase or decrease, but not below the number of shares then outstanding;
- the voting rights, if any, of the holders of the series;

- whether dividends, if any, will be cumulative or non-cumulative and the dividend rate of the series;
- the dates at which dividends, if any, will be payable;
- the rights of priority and amounts payable, if any, on shares of the series in the event of any voluntary or involuntary liquidation, dissolution or winding-up of the affairs of our company;
- the redemption rights and price or prices, if any, for shares of the series;
- the terms of any purchase, retirement or sinking fund, if any, provided for shares of the series;
- the terms, if any, upon which the shares of the series will be convertible into or exchangeable for shares of any other class, classes or series or other securities, whether or not issued by our company or any other entity;
- restrictions, if any, upon issuance of indebtedness of our company so long as any shares of the series are outstanding; and
- restrictions, if any, on the issuance of shares of the same series or of any other class or series.

We could issue a series of preferred stock that could, depending on the terms of the series, impede or discourage an acquisition attempt or other transaction that some, or a majority, of our stockholders might believe to be in their best interests or in which our stockholders might receive a premium for their shares of common stock over the market price of the shares of common stock.

Options

As of March 31, 2018 we had 2,427,629 options to purchase our common stock outstanding. See "*Executive and Director Compensation—Employee Benefit and Stock Plans*" for a discussion of the terms of the Plan.

Authorized but Unissued Capital Stock

The DGCL does not require stockholder approval for any issuance of authorized shares. However, the listing requirements of Nasdaq, which apply so long as our common stock remains listed on Nasdaq, require stockholder approval of certain issuances equal to or exceeding 20% of the then outstanding voting power or then outstanding number of shares of common stock. These additional shares may be used for a variety of corporate purposes, including future public offerings, to raise additional capital or to facilitate acquisitions.

One of the effects of the existence of unissued and unreserved common stock or preferred stock may be to enable our board of directors to issue shares to persons friendly to current management, which issuance could render more difficult or discourage an attempt to obtain control of our company by means of a merger, tender offer, proxy contest or otherwise, and thereby protect the continuity of our management and possibly deprive our stockholders of opportunities to sell their shares of common stock at prices higher than prevailing market prices.

Anti-Takeover Effects of Provisions of Delaware Law and Our Amended and Restated Certificate of Incorporation and Amended and Restated Bylaws

Undesignated Preferred Stock

The ability to authorize undesignated preferred stock will make it possible for our board of directors to issue preferred stock with super voting, special approval, dividend or other rights or preferences on a discriminatory basis that could impede the success of any attempt to acquire us or otherwise effect a change in control of us. These and other provisions may have the effect of deferring, delaying or discouraging hostile takeovers, or changes in control or management of our company.

Requirements for Advance Notification of Stockholder Meetings, Nominations and Proposals

Our amended and restated certificate of incorporation provides that special meetings of the stockholders may be called only by or at the direction of our board of directors. Our amended and restated bylaws prohibit the conduct of any business at a special meeting other than as specified in the notice for such meeting. These provisions may have the effect of deferring, delaying or discouraging hostile takeovers, or changes in control or management of our company.

Our amended and restated bylaws establish advance notice procedures with respect to stockholder proposals and the nomination of candidates for election as directors, other than nominations made by or at the direction of the board of directors or a committee of the board of directors. In order for any matter to be "properly brought" before a meeting, a stockholder will have to comply with advance notice requirements and provide us with certain information. Additionally, vacancies and newly created directorships may be filled only by a vote of a majority of the directors then in office, even though less than a quorum, and not by the stockholders. Our amended and restated bylaws allow the presiding officer at a meeting of the stockholders to adopt rules and regulations for the conduct of meetings which may have the effect of precluding the conduct of certain business at a meeting if the rules and regulations are not followed. These provisions may also defer, delay or discourage a potential acquirer from conducting a solicitation of proxies to elect the acquirer's own slate of directors or otherwise attempting to obtain control of our company.

Our amended and restated certificate of incorporation provides that the board of directors is expressly authorized to adopt, amend or repeal our amended and restated bylaws.

No Cumulative Voting

The DGCL provides that stockholders are not entitled to cumulate votes in the election of directors unless our amended and restated certificate of incorporation provides otherwise. Our amended and restated certificate of incorporation does not expressly provide for cumulative voting.

Removal of Directors

In accordance with the terms of our amended and restated certificate of incorporation and amended and restated bylaws, our board of directors are divided into three staggered classes of directors of the same or nearly the same number. At each annual meeting of the stockholders, a class of directors will be elected for a three-year term to succeed the directors of the same class whose terms are then expiring.

- Our Class I directors are Keith Gottesdiener and Christophe Jean, whose terms expire in 2021;
- Our Class II directors are Ed Mathers, Todd Foley, and Neil Exter, whose terms expire in 2019; and
- Our Class III directors are David Meeker and David McGirr, whose terms expire in 2020.

Our amended and restated certificate of incorporation and amended and restated bylaws provide that the number of our directors shall be fixed from time to time by a resolution of the majority of our board of directors. Any additional directorships resulting from an increase in the number of directors will be distributed among the three classes so that, as nearly as possible, each class shall consist of one third of the board of directors.

The division of our board of directors into three classes with staggered three-year terms may delay or prevent stockholder efforts to effect a change of our management or a change in control.

Our amended and restated certificate of incorporation and amended and restated bylaws provide that our directors may be removed only for cause by the affirmative vote of the holders of at least 75% of the outstanding shares of capital stock entitled to vote in the election of directors or class of directors, voting together as a single class, at a meeting of the stockholders called for that purpose. This requirement of a supermajority vote to remove directors could enable a minority of our stockholders to prevent a change in the composition of our board. Any vacancy on our board of directors, including a vacancy resulting from an enlargement of our board of directors, may be filled only by the vote of a majority of the remaining directors then in office, although less than a quorum, or by the sole remaining director.

Amendments to Amended and Restated Certificate of Incorporation and Amended and Restated Bylaws

The DGCL provides that, unless a corporation's certificate of incorporation provides otherwise, the affirmative vote of holders of shares constituting a majority of the votes of all shares entitled to vote may approve amendments to the certificate of incorporation.

Our amended and rested certificate of incorporation and amended and restated bylaws provide that the affirmative vote of holders of at least 75% of the outstanding shares of capital stock, voting together as a single class, and entitled to vote in the election of directors will be required to amend, alter, change or repeal the amended and restated certificate of incorporation and the amended and restated bylaws. This requirement of a supermajority vote to approve amendments to our amended and restated certificate of incorporation and amended and restated bylaws could enable a minority of our stockholders to exercise veto power over such amendments.

Stockholder Action by Written Consent

Pursuant to Section 228 of the DGCL, any action required to be taken at any annual or special meeting of the stockholders may be taken without a meeting, without prior notice and without a vote if a consent or consents in writing, setting forth the action so taken, is signed by the holders of outstanding stock having not less than the minimum number of votes that would be necessary to authorize or take such action at a meeting at which all shares of our stock entitled to vote thereon were present and voted, unless the corporation's certificate of incorporation provides otherwise. Our amended and restated certificate of incorporation prohibits the taking of any action of our stockholders by written consent without a meeting.

Delaware Anti-Takeover Statute

We have not opted out of, and therefore are subject to, Section 203 of the DGCL. Section 203 provides that, subject to certain exceptions specified in the law, a publicly-held Delaware corporation shall not engage in certain "business combinations" with any "interested stockholder" for a three-year period after the date of the transaction in which the person became an interested stockholder unless:

- prior to the date of the transaction, the board of directors of the corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder;

- upon completion of the transaction that resulted in the stockholder becoming an interested stockholder, the stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the number of shares outstanding (1) shares owned by persons who are directors and also officers and (2) shares owned under employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or

- on or subsequent to the date of the transaction, the business combination is approved by the board and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least $66^2/3$% of the outstanding voting stock which is not owned by the interested stockholder.

Generally, a business combination includes a merger, asset or stock sale, or other transaction resulting in a financial benefit to the interested stockholder. An interested stockholder is a person who, together with affiliates and associates, owns or, within three years prior to the determination of interested stockholder status, did own 15% or more of a corporation's outstanding voting stock. Since Section 203 will apply to us, we expect that it would have an anti-takeover effect with respect to transactions our board of directors does not approve in advance. In such event, we would also anticipate that Section 203 could discourage attempts that might result in a premium over the market price for the shares of common stock held by stockholders.

Under certain circumstances, Section 203 makes it more difficult for a person who would be an "interested stockholder" to effect various business combinations with a corporation for a three-year period. The provisions of Section 203 may encourage companies interested in acquiring our company to negotiate in advance with our board of directors because the stockholder approval requirement would be avoided if our board of directors approves either the business combination or the transaction that results in the stockholder becoming an interested stockholder. These provisions also may make it more difficult to accomplish transactions that stockholders may otherwise deem to be in their best interests.

Registration Rights

As of March 31, 2018, the holders of approximately 18.9 million shares of our common stock, or their transferees, are entitled to the registration rights set forth below with respect to registration of the resale of such shares under the Securities Act pursuant to the investors' rights agreement, by and among us and certain of our stockholders.

Demand Registration Rights

Upon the written request of at least a majority of the holders of the registrable securities then outstanding that we file a registration statement under the Securities Act covering the registration of registrable securities owned by such holder(s) having an anticipated aggregate offering price, net of selling expenses, of at least $15.0 million, we will be obligated to notify all holders of registrable securities of such request. As soon as practicable thereafter, and in any event within 60 days after the date such request is received, we will be required to register the sale on a registration statement on Form S-1 of all registrable securities that holders may request to be registered, subject to specified exceptions, conditions and limitations. We may postpone the filing of a registration statement for up to 120 days once in any 12-month period if in the good faith judgment of our board of directors such registration would be materially detrimental to us, and we are not required to effect the filing of a registration statement during the period starting with the date that is 60 days prior to our good faith estimate of the date of filing of a registration statement initiated by us and ending on a date 180 days after the effective date of a registration statement initiated by us. The underwriters of any underwritten offering will have the right to limit the number of shares having registration rights to be included in the registration statement.

"Piggyback" Registration Rights

If we register any securities for public sale, holders of registration rights will have the right to include their shares in the registration statement. The underwriters of any underwritten offering will have the right to limit the number of registrable securities to be included in the registration statement, but such number may not be below 30% of the total number of shares included in such registration statement. The holders of registration rights have waived any and all rights to which they would otherwise be entitled to have their shares included in this offering.

Form S-3 Registration Rights

If we are eligible to file a registration statement on Form S-3, holders of at least 10% of our registrable securities then outstanding have the right to request that we file a registration statement on Form S-3, so long as the aggregate price to the public of the securities to be sold under the registration statement on Form S-3 is at least $10.0 million or consists of all the remaining registrable securities, and subject to specified exceptions, conditions and limitations.

Expenses of Registration

Pursuant to the investors' rights agreement, we are generally required to bear all registration expenses, including the fees and expenses of one counsel, not to exceed $50,000, representing the selling holders, incurred in connection with the demand, piggyback and Form S-3 registrations described above. We are not required to bear selling expenses, which include all underwriting discounts, selling commissions, stock transfer taxes applicable to the sale of registrable securities and fees and disbursements of any additional counsel for any selling holder. We are not required to pay registration expenses if the registration request under the investors' rights agreement is withdrawn at the request of the holders of a majority of the registrable securities unless (i) the holders of a majority of the registrable securities then outstanding agree to forfeit their right to one registration under the investors' rights agreement or (ii) the withdrawal is due to the discovery of a material adverse change in our business.

Termination of Registration Rights

The demand, piggyback and Form S-3 registration rights discussed above will terminate as to a given holder of registrable securities upon the earlier of (i) five years following the closing of our initial public offering or (ii) such time as SEC Rule 144 or another similar exemption under the Securities Act is available for the sale of all shares held by the holder during a three-month period without registration and without the requirement for us to be in compliance with the current public information required under SEC Rule 144(c)(1).

Limitations of Liability and Indemnification

See "*Executive and Director Compensation—Limitation on Liability and Indemnification Matters*."

Market Listing

Our common stock is listed on the Nasdaq Global Market under the symbol "RYTM."

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Computershare Trust Company, Inc. The transfer agent and registrar's address is 250 Royall Street, Canton, MA 02021.

MATERIAL UNITED STATES FEDERAL INCOME AND ESTATE TAX CONSEQUENCES TO NON-U.S. HOLDERS OF OUR COMMON STOCK

The following is a discussion of the material U.S. federal income and estate tax consequences of the acquisition, ownership, and disposition of our common stock to a non-U.S. holder that purchases shares of our common stock for cash in this offering. For purposes of this discussion, a "non-U.S. holder" means a beneficial owner (other than a partnership or other pass-through entity) of our common stock that is not, for U.S. federal income tax purposes:

- an individual who is a citizen or resident alien of the United States;
- a corporation or any other organization taxable as a corporation for U.S. federal income tax purposes, created or organized in the United States or under the laws of the United States or of any state thereof or the District of Columbia;
- an estate, the income of which is subject to U.S. federal income tax regardless of its source; or
- a trust if (i) the trust is subject to the primary supervision of a U.S. court and all substantial decisions of the trust are controlled by one or more U.S. persons or (ii) the trust has a valid election in effect under applicable U.S. Treasury regulations to be treated as a U.S. person.

This discussion does not address the tax treatment of partnerships (or other entities that are treated as partnerships, grantor trusts, or other pass-through entities for U.S. federal income tax purposes) or persons that hold their common stock through partnerships, grantor trusts or such other pass-through entities. The tax treatment of a partner in a partnership or a holder of an interest in another pass-through entity that will hold our common stock generally will depend upon the status of the partner or interest holder and the activities of the partner or interest holder and the partnership or other pass-through entity, as applicable. Such a partner or interest holder should consult his, her, or its own tax advisor regarding the tax consequences of the acquisition, ownership and disposition of our common stock through a partnership or other pass-through entity, as applicable.

This discussion is based upon the provisions of the Code, the U.S. Treasury regulations promulgated thereunder, judicial decisions, and published rulings, administrative procedures and other guidance of the Internal Revenue Service, which we refer to as the IRS, all as in effect as of the date hereof. These authorities are subject to change and to differing interpretations, possibly with retroactive effect, which could result in U.S. federal income or estate tax consequences different from those summarized below. No ruling has been or will be sought from the IRS with respect to the matters summarized below, and there can be no assurance that the IRS will not take a contrary position regarding the U.S. federal income or estate tax consequences of the acquisition, ownership, or disposition of our common stock, or that any such contrary position would not be sustained by a court.

This discussion is not a complete analysis of all of the potential U.S. federal income and estate tax consequences relating to the acquisition, ownership, and disposition of our common stock by non-U.S. holders, nor does it address any U.S. federal gift tax or generation-skipping transfer tax consequences, any tax consequences arising under any state, local, or non-U.S. tax laws, the impact of any applicable tax treaty, any consequences under the Medicare contribution tax on net investment income, the alternative minimum tax, or any consequences under other U.S. federal tax laws. In addition, this discussion does not address tax consequences resulting from a non-U.S. holder's particular circumstances or to non-U.S. holders that may be subject to special tax rules, including, without limitation:

- non-U.S. governments, agencies or instrumentalities thereof, or entities they control;
- "controlled foreign corporations" and their shareholders;
- "passive foreign investment companies" and their shareholders;

- partnerships, grantor trusts or other entities that are treated as pass-through entities for U.S. federal income tax purposes, and their owners;
- corporations that accumulate earnings to avoid U.S. federal income tax;
- former citizens or former long-term residents of the United States;
- banks, insurance companies or other financial institutions;
- tax-exempt pension funds or other tax-exempt organizations;
- persons who acquired our common stock pursuant to the exercise of employee stock options or otherwise as compensation;
- tax-qualified retirement plans;
- traders, brokers or dealers in securities, commodities or currencies;
- persons who hold our common stock as a position in a hedging transaction, wash sale, "straddle," "conversion transaction" or other risk reduction transaction or synthetic security;
- persons who do not hold our common stock as a capital asset within the meaning of Section 1221 of the Code (generally, for investment purposes);
- persons who own or have owned, or are deemed to own or to have owned, more than 5% of our common stock (except to the extent specifically set forth below); or
- persons deemed to sell our common stock under the constructive sale provisions of the Code.

Prospective investors should consult their tax advisors regarding the particular U.S. federal income, estate, gift, and generation-skipping transfer tax consequences to them of acquiring, owning and disposing of our common stock, as well as any tax consequences arising under any state, local or foreign tax laws and any other U.S. federal tax laws. Prospective investors should also consult their tax advisors regarding the potential impact of any applicable income or estate tax treaty between the United States and such prospective investor's country of residence and of the rules described below under the heading "Foreign Account Tax Compliance Act."

Distributions on Common Stock

As described in the section entitled "Dividend Policy," we currently intend to retain all available funds and any future earnings for use in the operation of our business and do not anticipate paying any dividends on our common stock in the foreseeable future. The disclosure in this section addresses the consequences should our board of directors, in the future, determine to make a distribution of cash or property with respect to our common stock (other than certain distributions of stock which may be made free of tax), or to effect a redemption that is treated for tax purposes as a distribution. Any such distribution will generally constitute a dividend for U.S. federal tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. To the extent such a distribution exceeds both our current and our accumulated earnings and profits, such excess will be allocated ratably among the shares of common stock with respect to which the distribution is made, will constitute a return of capital, and will first be applied against and reduce the non-U.S. holder's adjusted tax basis in those shares of common stock, but not below zero. Distributions in excess of our current and accumulated earnings and profits and in excess of a non-U.S. holder's tax basis in that non-U.S. holder's shares of common stock then will be treated as gain from the sale of that common stock, subject to the tax treatment described below under "Gain on Disposition of Common Stock." A non-U.S. holder's adjusted tax basis in a share of common stock is generally the purchase price of the share, reduced by the amount of any distributions constituting a return of capital with respect to that share.

Any dividend paid to a non-U.S. holder of our common stock generally will be subject to U.S. federal withholding tax at a rate of 30% of the gross amount of the dividend, or such lower rate as may be specified by an applicable income tax treaty between the United States and such non-U.S. holder's country of residence. If a non-U.S. holder is eligible for benefits under an income tax treaty and wishes to claim a reduced rate of withholding, the non-U.S. holder generally will be required to provide us or our paying agent with a properly completed IRS Form W-8BEN, Form W-8BEN-E, or other applicable form, certifying under penalties of perjury the non-U.S. holder's qualification for the reduced rate. This certification must be provided to us or our paying agent prior to the payment of the dividend and may be required to be updated periodically. Special certification requirements apply to non-U.S. holders that hold common stock through certain foreign intermediaries. Non-U.S. holders that do not timely provide the required certifications, but that qualify for a reduced treaty rate, may obtain a refund of any excess amounts withheld by timely filing an appropriate claim for refund with the IRS. If we are not able to determine whether or not a distribution will exceed current and accumulated earnings and profits at the time the distribution is made, we may withhold tax on the entire amount of any distribution at the same rate as we would withhold on a dividend. However, a non-U.S. holder may obtain a refund of amounts that we withhold to the extent attributable to the portion of the distribution in excess of our current and accumulated earnings and profits.

If a non-U.S. holder holds our common stock in connection with the conduct of a trade or business in the U.S., and dividends paid on the common stock are effectively connected with the non-U.S. holder's U.S. trade or business (and, if required by an applicable income tax treaty between the United States and such non-U.S. holder's country of residence, are attributable to a permanent establishment or fixed base maintained by the non-U.S. holder in the U.S., as defined under the applicable treaty), the non-U.S. holder will be exempt from U.S. federal withholding tax on the dividends. To claim the exemption, the non-U.S. holder must furnish a properly executed IRS Form W-8ECI (or other applicable form) prior to the payment of the dividends. Any dividends paid on our common stock that are effectively connected with a non-U.S. holder's U.S. trade or business (and satisfy any other applicable treaty requirements) generally will be subject to U.S. federal income tax on a net income basis at the regular graduated U.S. federal income tax rates generally applicable to U.S. persons (as defined in the Code). A non-U.S. holder that is treated as a corporation for U.S. federal income tax purposes also may be subject to an additional branch profits tax equal to 30% (or such lower rate as is specified by an applicable income tax treaty between the United States and such non-U.S. holder's country of residence) of a portion of its earnings and profits for the taxable year that are effectively connected with a U.S. trade or business, as adjusted for certain items.

Gain on Disposition of Common Stock

Subject to the discussion below regarding backup withholding and foreign accounts, a non-U.S. holder generally will not be subject to U.S. federal income tax on any gain realized upon the sale, exchange, or other taxable disposition of our common stock unless:

- the gain is effectively connected with the non-U.S. holder's conduct of a U.S. trade or business (and, if required by an applicable income tax treaty between the United States and such non-U.S. holder's country of residence, the gain is attributable to a permanent establishment or fixed base maintained by the non-U.S. holder in the United States), in which case the non-U.S. holder will generally be required to pay tax on the gain derived from the sale, exchange, or other taxable disposition (net of certain deductions or credits) under regular graduated U.S. federal income tax rates generally applicable to U.S. persons, and in the case of a non-U.S. holder that is treated as a corporation for U.S. federal income tax purposes, such non-U.S. holder may be subject to a branch profits tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and such non-U.S. holder's country of residence;

- the non-U.S. holder is an individual who is present in the U.S. for a period or periods aggregating 183 days or more during the taxable year in which the sale, exchange, or other taxable disposition occurs and certain other conditions are met, in which case the non-U.S. holder will be subject to U.S. federal income tax at a flat 30% rate (or such lower rate as is specified by an applicable income tax treaty between the United States and such non-U.S. holder's country of residence) on the net gain derived from the sale, exchange, or other taxable disposition, which gain may be offset by U.S. source capital losses (even though the non-U.S. holder is not considered a resident of the United States) provided that the non-U.S. holder has timely filed U.S. federal income tax returns reporting those losses; or

- our common stock is a "United States real property interest" by reason of our status as a "United States real property holding corporation," or USRPHC, for U.S. federal income tax purposes during the five-year period preceding such sale, exchange or other taxable disposition (or the non-U.S. holder's holding period, if shorter). Generally, a corporation is a USRPHC only if the fair market value of its U.S. real property interests equals or exceeds 50% of the sum of the fair market value of its worldwide real property interests plus its other assets used or held for use in a trade or business.

We believe we are not now and we do not anticipate becoming a USRPHC. However, there can be no assurance that we are not now a USRPHC or will not become one in the future. Even if we are or become a USRPHC, for so long as our common stock is "regularly traded," as defined by applicable U.S. Treasury regulations, on an established securities market, sales of our common stock generally will not be subject to tax for non-U.S. holders that have not held more than 5% of our common stock, actually or constructively, during the five-year period preceding such non-U.S. holder's sale, exchange or other taxable disposition of our common stock (or the non-U.S. holder's holding period, if shorter). If we are determined to be a USRPHC and the foregoing exception does not apply, then the non-U.S. holder generally will be taxed on its net gain derived from the disposition at the graduated U.S. federal income tax rates applicable to U.S. persons. No assurance can be provided that our common stock will be regularly traded on an established securities market for purposes of the rule described above.

U.S. Federal Estate Tax

Shares of our common stock that are owned or treated as owned at the time of death by an individual who is not a citizen or resident of the United States, as specifically defined for U.S. federal estate tax purposes, are considered U.S. situs assets and will be included in the individual's gross estate for U.S. federal estate tax purposes. Such shares, therefore, may be subject to U.S. federal estate tax, unless an applicable estate tax or other treaty between the United States and such individual's country of residence provides otherwise.

Information Reporting and Backup Withholding

Generally, we or certain financial middlemen must report annually to the IRS and to each non-U.S. holder the gross amount of dividends and other distributions on our common stock paid to the non-U.S. holder and the amount of tax withheld, if any, with respect to those distributions. Pursuant to applicable income tax treaties or other agreements, the IRS may make these reports available to tax authorities in the non-U.S. holder's country of residence or incorporation.

A non-U.S. holder may be subject to backup withholding with respect to dividends paid on shares of our common stock, unless, generally, the non-U.S. holder certifies under penalties of perjury (usually on IRS Form W-8BEN or W-8BEN-E) that the non-U.S. holder is not a U.S. person or otherwise establishes an exemption. The backup withholding rate is currently 24%. Dividends that are paid to non-U.S. holders subject to the withholding of U.S. federal income tax, as described above under the heading "Distributions on Common Stock" generally will be exempt from U.S. backup withholding.

Additional rules relating to information reporting requirements and backup withholding with respect to payments of the proceeds from the disposition of shares of our common stock are as follows:

- If the proceeds are paid to or through the U.S. office of a broker, the proceeds generally will be subject to backup withholding and information reporting, unless the non-U.S. holder certifies under penalties of perjury (usually on IRS Form W-8BEN or W-8BEN-E) that the non-U.S. holder is not a U.S. person and satisfies certain other requirements or otherwise establishes an exemption.

- If the proceeds are paid to or through a non-U.S. office of a broker that is not a U.S. person and is not a foreign person with certain specified U.S. connections, which we refer to below as a "U.S.-related person," information reporting and backup withholding generally will not apply.

- If the proceeds are paid to or through a non-U.S. office of a broker that is a U.S. person or a U.S.-related person, the proceeds generally will be subject to information reporting (but not to backup withholding), unless the non-U.S. holder certifies under penalties of perjury (usually on IRS Form W-8BEN or W-8BEN-E) that the non-U.S. holder is not a U.S. person. A "U.S.-related person" includes (i) an entity classified as a "controlled foreign corporation" for U.S. federal income tax purposes, (ii) a foreign person, 50% or more of whose gross income from certain periods is effectively connected with a U.S. trade or business, or (iii) a foreign partnership if at any time during its tax year (a) one or more of its partners are U.S. persons who, in the aggregate, hold more than 50% of the income or capital interests of the partnership or (b) the foreign partnership is engaged in a U.S. trade or business.

Backup withholding is not an additional tax. Any amounts withheld from a non-U.S. holder under the backup withholding rules may be allowed as a refund or a credit against the non-U.S. holder's U.S. federal income tax liability, if any, provided that the non-U.S. holder timely furnishes the required information to the IRS. Non-U.S. holders should consult their own tax advisors regarding the application of the information reporting and backup withholding rules to them.

Foreign Account Tax Compliance Act

Sections 1471 to 1474 of the Code (commonly referred to as the Foreign Account Tax Compliance Act, or FATCA) generally impose withholding tax on certain types of payments made to "foreign financial institutions" (as defined in the Code) and other non-U.S. entities unless those institutions and entities meet additional certification, information reporting and other requirements. FATCA generally imposes a 30% withholding tax on dividends on, or gross proceeds from the sale or other disposition of, our common stock paid to a foreign financial institution unless the foreign financial institution enters into an agreement with the U.S. Treasury to, among other things, (i) undertake to identify accounts held by certain U.S. persons (including certain equity and debt holders of such institution) or by U.S.-owned foreign entities, (ii) annually report certain information about such accounts, and (iii) withhold 30% on payments to account holders whose actions prevent it from complying with these reporting and other requirements. In addition, subject to certain exceptions, FATCA imposes a 30% withholding tax on the same types of payments to a "non-financial foreign entity" (as defined in the Code) unless the entity certifies that it does not have any substantial U.S. owners (which generally include any U.S. persons who directly or indirectly own more than 10% of the entity) or furnishes identifying information regarding each such substantial U.S. owner or agrees to report that information to the IRS. These withholding taxes will be imposed on dividends paid on our common stock, and, after December 31, 2018, on gross proceeds from sales or other dispositions of our common stock. Withholding under FATCA generally will not be reduced or limited by bilateral income tax treaties. However, intergovernmental agreements between the U.S. and other countries with respect to the implementation of FATCA and non-U.S. laws, regulations and other authorities enacted or issued with respect to those intergovernmental agreements may modify the FATCA requirements described above. Non-U.S. holders should consult their own tax advisors regarding the possible implications of FATCA on their investment in our common stock and the entities through which they hold our common stock, including, without limitation, the process and deadlines for meeting the applicable requirements to prevent the imposition of the 30% withholding tax under FATCA.

SHARES ELIGIBLE FOR FUTURE SALE

We cannot predict the effect, if any, that future sales of shares of common stock, or the availability for future sales of shares of common stock, will have on the market price of shares of our common stock prevailing from time to time. The sale of substantial amounts of shares of our common stock in the public market, or the perception that such sales could occur, could harm the prevailing market price of shares of our common stock.

Upon completion of this offering, we will have a total of 31,885,367 shares of our common stock outstanding (or 32,575,551 shares of common stock if the underwriters exercise in full their option to purchase additional shares of common stock), based upon the 27,284,140 shares of our common stock that were outstanding at March 31, 2018.

Of those shares, we expect that 19,409,120 shares, including the shares sold in this offering, will be freely tradeable without restriction under the Securities Act by persons other than our "affiliates." Under the Securities Act, an "affiliate" of an issuer is a person who directly or indirectly controls, is controlled by or is under common control with that issuer.

In addition, 5,109,904 shares of common stock may be granted under the 2017 Plan, which amount includes 2,427,629 shares subject to options outstanding as of March 31, 2018.

The remaining 12,476,247 shares of our common stock will be "restricted securities" under Rule 144. Of these shares, 886,112 shares will be subject to a 90-day lockup period and 11,590,135 shares will be subject to a 60-day lockup period under the lock-up agreements entered into in connection with this offering, as further described below. Upon expiration of the lock-up period, these restricted securities may be sold in the public market only if registered or pursuant to an exemption from registration, such as Rule 144 or Rule 701 under the Securities Act.

Our amended and restated certificate of incorporation authorizes us to issue additional shares of common stock and options, rights, warrants and appreciation rights relating to common stock for the consideration and on the terms and conditions established by our board of directors in its sole discretion. In accordance with the Delaware General Corporation Law and the provisions of our amended and restated certificate of incorporation, we may also issue preferred stock that has designations, preferences, rights, powers and duties that are different from, and may be senior to, those applicable to shares of common stock. See "*Description of Capital Stock.*"

Lock-Up Agreements

We, along with our directors, executive officers and certain of our other stockholders, have agreed with the underwriters that for a period of 90 days (the restricted period for our directors and executive officers) or 60 days (the restricted period for certain of our other stockholders) after the date of this prospectus, subject to specified exceptions, we or they will not offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend or otherwise transfer or dispose of, directly or indirectly, any shares of common stock or any securities convertible into or exercisable or exchangeable for shares of common stock, or enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of the common stock. Certain of our stockholders have the right to require us to register their shares under the Securities Act. See "*—Registration Rights"* below and *"Description of Capital Stock—Registration Rights."*

After this offering, our executive officers and/or directors may enter into written trading plans that are intended to comply with Rule 10b5-1 under the Securities Exchange Act of 1934, as amended, or the Exchange Act. Sales under these trading plans would not be permitted until the expiration of the lock-up agreements relating to the offering described above.

Registration Rights

The holders of approximately 18.9 million shares of our common stock are entitled to rights with respect to the registration of their shares under the Securities Act. Registration of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act, except for shares purchased by affiliates. Any sales of securities by these stockholders could have a material adverse effect on the trading price of our common stock. See "*Description of Capital Stock—Registration Rights*."

Rule 144

In general, under Rule 144 a person (or persons whose shares are aggregated) who may be deemed our affiliate is entitled to sell within any three-month period a number of restricted securities that does not exceed the greater of 1% of the then outstanding shares of common stock and the average weekly trading volume during the four calendar weeks preceding each such sale, provided that at least six months has elapsed since such shares of common stock were acquired from us or any affiliate of ours and certain manner of sale, notice requirements and requirements as to availability of current public information about us are satisfied. Any person who is deemed to be our affiliate must also comply with such provisions of Rule 144 (other than the six-month holding period requirement) in order to sell shares of common stock which are not restricted securities (such as shares of common stock acquired by affiliates through purchases in the open market following this offering). As of May 31, 2018, 19,419,684 shares of our common stock are "restricted securities" as such term is defined in Rule 144. A person who is not our affiliate, and who has not been our affiliate at any time during the 90 days preceding any sale, is entitled to sell shares of common stock (i) subject only to the requirements as to availability of current public information about us, provided that a period of at least six months has elapsed since the shares of common stock were acquired from us or any affiliate of ours, and (ii) without regard to the requirements as to availability of current public information about us or any other requirement of Rule 144, provided that at least one year has elapsed since the shares of common stock were acquired from us or any affiliate of ours.

Rule 701

In general, under Rule 701 of the Securities Act, any of our employees, consultants or advisors, other than our affiliates, who purchased shares from us in connection with a qualified compensatory stock plan or other written agreement before our initial public offering is eligible to resell these shares in reliance on Rule 144, but without compliance with the holding period requirements of Rule 144 and without regard to the volume of such sales or the availability of public information about us.

UNDERWRITING

Under the terms and subject to the conditions in an underwriting agreement dated the date of this prospectus, the underwriters named below, for whom Morgan Stanley & Co. LLC, Merrill Lynch, Pierce, Fenner & Smith Incorporated and Cowen and Company, LLC are acting as representatives, have severally agreed to purchase, and we have agreed to sell to them, severally, the number of shares indicated below:

Underwriter	Number of Shares
Morgan Stanley & Co. LLC	
Merrill Lynch, Pierce, Fenner & Smith Incorporated	
Cowen and Company, LLC	
Needham & Company, LLC	
Total	4,601,227

The underwriters and the representatives are collectively referred to as the "underwriters" and the "representatives," respectively. The underwriters are offering the shares of common stock subject to their acceptance of the shares from us and subject to prior sale. The underwriting agreement provides that the obligations of the several underwriters to pay for and accept delivery of the shares of common stock offered by this prospectus are subject to the approval of certain legal matters by their counsel and to certain other conditions. The underwriters are obligated to take and pay for all of the shares of common stock offered by this prospectus if any such shares are taken. However, the underwriters are not required to take or pay for the shares covered by the underwriters' option to purchase additional shares described below.

The underwriters initially propose to offer part of the shares of common stock directly to the public at the offering price listed on the cover page of this prospectus and part to certain dealers. After the initial offering of the shares of common stock, the offering price and other selling terms may from time to time be varied by the representatives.

We have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus, to purchase up to $22.5 million of additional shares of common stock at the public offering price listed on the cover page of this prospectus, less underwriting discounts and commissions. To the extent the option is exercised, each underwriter will become obligated, subject to certain conditions, to purchase about the same percentage of the additional shares of common stock as the number listed next to the underwriter's name in the preceding table bears to the total number of shares of common stock listed next to the names of all underwriters in the preceding table.

The following table shows the per share and total public offering price, underwriting discounts and commissions, and proceeds before expenses to us. These amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase up to an additional $22.5 million of shares of common stock.

		Total	
	Per Share	No Exercise	Full Exercise
Public offering price	$	$	$
Underwriting discounts and commissions to be paid by us	$	$	$
Proceeds, before expenses, to us	$	$	$

The estimated offering expenses payable by us, exclusive of the underwriting discounts and commissions, are approximately $740,000. We have agreed to reimburse the underwriters for expenses relating to clearance of this offering with the Financial Industry Regulatory Authority up to $40,000.

The underwriters have informed us that they do not intend sales to discretionary accounts to exceed 5% of the total number of shares of common stock offered by them.

Our common stock is listed on the Nasdaq Global Market under the trading symbol "RYTM."

We and all directors, executive officers and certain stockholders have agreed that, without the prior written consent of Morgan Stanley & Co. LLC, Merrill Lynch, Pierce, Fenner & Smith Incorporated and Cowen and Company, LLC on behalf of the underwriters, we and they will not, during the period ending 90 days after the date of this prospectus for us and our directors and executive officers and during the period ending 60 days after the date of this prospectus for certain of our stockholders, the restricted period:

- offer, sell, contract to sell, pledge or otherwise dispose of, (or enter into any transaction which is designed to, or might reasonably be expected to, result in the disposition (whether by actual disposition or effective economic disposition due to cash settlement or otherwise), directly or indirectly) any capital stock or any securities convertible into, or exercisable or exchangeable for such capital stock;

- file any registration statement with the SEC (other than a registration statement on Form S-8) relating to the offering of any shares of capital stock or any securities convertible into or exercisable or exchangeable for capital stock; or

- establish or increase a put equivalent position or liquidate or decrease a call equivalent position within the meaning of Section 16 of the Exchange Act and the rules and regulations of the SEC promulgated thereunder with respect to any shares of capital stock or any securities convertible into or exercisable or exchangeable for capital stock;

whether any such transaction described above is to be settled by delivery of common stock or such other securities, in cash or otherwise. In addition, we and each such person agrees that, without the prior written consent of Morgan Stanley & Co. LLC, Merrill Lynch, Pierce, Fenner & Smith Incorporated and Cowen and Company, LLC on behalf of the underwriters, we or such other person will not, during the restricted period, make any demand for, or exercise any right with respect to, the registration of any shares of common stock or any security convertible into or exercisable or exchangeable for common stock.

The restrictions described in the immediately preceding paragraph do not apply to:

- the sale of shares to the underwriters;

- the issuance by us of shares of common stock upon the exercise of an option or a warrant or the conversion of a security outstanding on the date of this prospectus of which the underwriters have been advised in writing;

- transactions by any person other than us relating to shares of common stock or other securities acquired in open market transactions after the completion of the offering of the shares; provided that no filing under Section 16(a) of the Exchange Act is required or voluntarily made in connection with subsequent sales of the common stock or other securities acquired in such open market transactions; or

- the establishment of a trading plan pursuant to Rule 10b5-1 under the Exchange Act for the transfer of shares of common stock, provided that (i) such plan does not provide for the transfer of common stock during the restricted period and (ii) to the extent a public announcement or filing under the Exchange Act, if any, is required or voluntarily made regarding the establishment of such plan, such announcement or filing shall include a statement to the effect that no transfer of common stock may be made under such plan during the restricted period.

Morgan Stanley & Co. LLC, Merrill Lynch, Pierce, Fenner & Smith Incorporated and Cowen and Company, LLC, in their sole discretion, may release the common stock and other securities subject to the lock-up agreements described above in whole or in part at any time.

In order to facilitate the offering of the common stock, the underwriters may engage in transactions that stabilize, maintain or otherwise affect the price of the common stock. Specifically, the underwriters may sell more shares than they are obligated to purchase under the underwriting agreement, creating a short position. A short sale is covered if the short position is no greater than the number of shares available for purchase by the underwriters under the option. The underwriters can close out a covered short sale by exercising the option or purchasing shares in the open market. In determining the source of shares to close out a covered short sale, the underwriters will consider, among other things, the open market price of shares compared to the price available under the option. The underwriters may also sell shares in excess of the option, creating a naked short position. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market after pricing that could adversely affect investors who purchase in this offering. As an additional means of facilitating this offering, the underwriters may bid for, and purchase, shares of common stock in the open market to stabilize the price of the common stock. These activities may raise or maintain the market price of the common stock above independent market levels or prevent or retard a decline in the market price of the common stock. The underwriters are not required to engage in these activities and may end any of these activities at any time.

We and the underwriters have agreed to indemnify each other against certain liabilities, including liabilities under the Securities Act.

A prospectus in electronic format may be made available on websites maintained by one or more underwriters, or selling group members, if any, participating in this offering. The representatives may agree to allocate a number of shares of common stock to underwriters for sale to their online brokerage account holders. Internet distributions will be allocated by the representatives to underwriters that may make Internet distributions on the same basis as other allocations.

The underwriters and their respective affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, investment research, principal investment, hedging. financing and brokerage activities. Certain of the underwriters and their respective affiliates have, from time to time, performed, and may in the future perform, various financial advisory and investment banking services for us, for which they received or will receive customary fees and expenses.

In addition, in the ordinary course of their various business activities, the underwriters and their respective affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers and may at any time hold long and short positions in such securities and instruments. Such investment and securities activities may involve our securities and instruments. The underwriters and their respective affiliates may also make investment recommendations or publish or express independent research views in respect of such securities or instruments and may at any time hold, or recommend to clients that they acquire, long or short positions in such securities and instruments.

Pricing of the Offering

The public offering price was determined by negotiations between us and the representatives. Among the factors considered in determining the public offering price were our future prospects and those of our industry in general, our sales, earnings and certain other financial and operating information in recent periods, and the price-earnings ratios, price-sales ratios, market prices of securities, and certain financial and operating information of companies engaged in activities similar to ours.

Selling Restrictions

European Economic Area

In relation to each Country of the European Economic Area which has implemented the Prospectus Directive, each, a Relevant Country, an offer to the public of any shares of our common stock may not be made in that Relevant Country, except that an offer to the public in that Relevant Country of any shares of our common stock may be made at any time under the following exemptions under the Prospectus Directive, if they have been implemented in that Relevant Country:

(a) to any legal entity which is a qualified investor as defined in the Prospectus Directive;

(b) to fewer than 100 or, if the Relevant Country has implemented the relevant provision of the 2010 PD Amending Directive, 150, natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the representatives for any such offer; or

(c) in any other circumstances falling within Article 3(2) of the Prospectus Directive, provided that no such offer of shares of our common stock shall result in a requirement for the publication by us or any underwriter of a prospectus pursuant to Article 3 of the Prospectus Directive.

For the purposes of this provision, the expression an "offer to the public" in relation to any shares of our common stock in any Relevant Country means the communication in any form and by any means of sufficient information on the terms of the offer and any shares of our common stock to be offered so as to enable an investor to decide to purchase any shares of our common stock, as the same may be varied in that Relevant Country by any measure implementing the Prospectus Directive in that Relevant Country, the expression "Prospectus Directive" means Directive 2003/71/EC (and amendments thereto, including the 2010 PD Amending Directive, to the extent implemented in the Relevant Country), and includes any relevant implementing measure in the Relevant Country, and the expression "2010 PD Amending Directive" means Directive 2010/73/EU.

United Kingdom

Each underwriter has represented and agreed that:

(a) it has only communicated or caused to be communicated and will only communicate or cause to be communicated an invitation or inducement to engage in investment activity (within the meaning of Section 21 of the Financial Services and Markets Act 2000, or FSMA, received by it in connection with the issue or sale of the shares of our common stock in circumstances in which Section 21(1) of the FSMA does not apply to us; and

(b) it has complied and will comply with all applicable provisions of the FSMA with respect to anything done by it in relation to the shares of our common stock in, from or otherwise involving the United Kingdom.

Canada

The shares may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 Prospectus Exemptions or subsection 73.3(1) of the Securities Act (Ontario), and are permitted clients, as defined in National Instrument 31-103 Registration Requirements, Exemptions and Ongoing Registrant Obligations. Any resale of the shares must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 (or, in the case of securities issued or guaranteed by the government of a non-Canadian jurisdiction, section 3A.4) of National Instrument 33-105 Underwriting Conflicts (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

Notice to Prospective Investors in Switzerland

The shares may not be publicly offered in Switzerland and will not be listed on the SIX Swiss Exchange, or SIX, or on any other stock exchange or regulated trading facility in Switzerland. This document has been prepared without regard to the disclosure standards for issuance prospectuses under art. 652a or art. 1156 of the Swiss Code of Obligations or the disclosure standards for listing prospectuses under art. 27 ff. of the SIX Listing Rules or the listing rules of any other stock exchange or regulated trading facility in Switzerland. Neither this document nor any other offering or marketing material relating to the shares or the offering may be publicly distributed or otherwise made publicly available in Switzerland.

Neither this document nor any other offering or marketing material relating to the offering, the Company or the shares have been or will be filed with or approved by any Swiss regulatory authority. In particular, this document will not be filed with, and the offer of shares will not be supervised by, the Swiss Financial Market Supervisory Authority, or FINMA, and the offer of shares has not been and will not be authorized under the Swiss Federal Act on Collective Investment Schemes, or CISA. The investor protection afforded to acquirers of interests in collective investment schemes under the CISA does not extend to acquirers of shares.

Notice to Prospective Investors in the Dubai International Financial Centre

This prospectus relates to an Exempt Offer in accordance with the Offered Securities Rules of the Dubai Financial Services Authority, or DFSA. This prospectus is intended for distribution only to persons of a type specified in the Offered Securities Rules of the DFSA. It must not be delivered to, or relied on by, any other person. The DFSA has no responsibility for reviewing or verifying any documents in connection with Exempt Offers. The DFSA has not approved this prospectus nor taken steps to verify the information set forth herein and has no responsibility for the prospectus. The shares to which this prospectus relates may be illiquid and/or subject to restrictions on their resale. Prospective purchasers of the shares offered should conduct their own due diligence on the shares. If you do not understand the contents of this prospectus you should consult an authorized financial advisor.

Notice to Prospective Investors in Singapore

This prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of Non-CIS Securities may not be circulated or distributed, nor may the Non-CIS Securities be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore, or SFA, (ii) to a relevant person pursuant to Section 275(1), or any person pursuant to Section 275(1A), and in accordance with the conditions specified in Section 275, of the SFA, or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA.

Where the Non-CIS Securities are subscribed or purchased under Section 275 of the SFA by a relevant person which is:

(a) a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or

(b) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary of the trust is an individual who is an accredited investor,

securities (as defined in Section 239(1) of the SFA) of that corporation or the beneficiaries' rights and interest (howsoever described) in that trust shall not be transferred within six months after that corporation or that trust has acquired the Non-CIS Securities pursuant to an offer made under Section 275 of the SFA except:

(a) to an institutional investor or to a relevant person defined in Section 275(2) of the SFA, or to any person arising from an offer referred to in Section 275(1A) or Section 276(4)(i)(B) of the SFA;

(b) where no consideration is or will be given for the transfer;

(c) where the transfer is by operation of law;

(d) as specified in Section 276(7) of the SFA; or

(e) as specified in Regulation 32 of the Securities and Futures (Offers of Investments) (Shares and Debentures) Regulations 2005 of Singapore.

Notice to Prospective Investors in Hong Kong

The securities have not been offered or sold and will not be offered or sold in Hong Kong, by means of any document, other than (a) to "professional investors" as defined in the Securities and Futures Ordinance (Cap. 571) of Hong Kong and any rules made under that Ordinance; or (b) in other circumstances which do not result in the document being a "prospectus" as defined in the Companies Ordinance (Cap. 32) of Hong Kong or which do not constitute an offer to the public within the meaning of that Ordinance. No advertisement, invitation or document relating to the securities has been or may be issued or has been or may be in the possession of any person for the purposes of issue, whether in Hong Kong or elsewhere, which is directed at, or the contents of which are likely to be accessed or read by, the public of Hong Kong (except if permitted to do so under the securities laws of Hong Kong) other than with respect to securities which are or are intended to be disposed of only to persons outside Hong Kong or only to "professional investors" as defined in the Securities and Futures Ordinance and any rules made under that Ordinance.

Notice to Prospective Investors in Japan

The securities have not been and will not be registered under the Financial Instruments and Exchange Law of Japan (Law No. 25 of 1948, as amended) and, accordingly, will not be offered or sold, directly or indirectly, in Japan, or for the benefit of any Japanese Person or to others for re-offering or resale, directly or indirectly, in Japan or to any Japanese Person, except in compliance with all applicable laws, regulations and ministerial guidelines promulgated by relevant Japanese governmental or regulatory authorities in effect at the relevant time. For the purposes of this paragraph, "Japanese Person" shall mean any person resident in Japan, including any corporation or other entity organized under the laws of Japan.

Notice to Prospective Investors in Australia

No placement document, prospectus, product disclosure statement or other disclosure document has been lodged with the Australian Securities and Investments Commission, in relation to the offering. This prospectus does not constitute a prospectus, product disclosure statement or other disclosure document under the Corporations Act 2001, or Corporations Act, and does not purport to include the information required for a prospectus, product disclosure statement or other disclosure document under the Corporations Act.

Any offer in Australia of the shares may only be made to persons, or Exempt Investors, who are "sophisticated investors" (within the meaning of section 708(8) of the Corporations Act), "professional investors" (within the meaning of section 708(11) of the Corporations Act) or otherwise pursuant to one or more exemptions contained in section 708 of the Corporations Act so that it is lawful to offer the shares without disclosure to investors under Chapter 6D of the Corporations Act.

The shares applied for by Exempt Investors in Australia must not be offered for sale in Australia in the period of 12 months after the date of allotment under the offering, except in circumstances where disclosure to investors under Chapter 6D of the Corporations Act would not be required pursuant to an exemption under section 708 of the Corporations Act or otherwise or where the offer is pursuant to a disclosure document which complies with Chapter 6D of the Corporations Act. Any person acquiring shares must observe such Australian on-sale restrictions.

This prospectus contains general information only and does not take account of the investment objectives, financial situation or particular needs of any particular person. It does not contain any securities recommendations or financial product advice. Before making an investment decision, investors need to consider whether the information in this prospectus is appropriate to their needs, objectives and circumstances, and, if necessary, seek expert advice on those matters.

LEGAL MATTERS

The validity of the shares of common stock offered hereby has been passed upon for us by Morgan, Lewis & Bockius LLP, Boston, Massachusetts. Certain legal matters in connection with this offering will be passed upon for the underwriters by Ropes and Gray LLP, Boston, Massachusetts.

EXPERTS

The consolidated financial statements of Rhythm Pharmaceuticals, Inc. at December 31, 2016 and 2017, and for each of the three years in the period ended December 31, 2017 appearing in this prospectus and the registration statement have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon appearing elsewhere herein, and are included in reliance upon such report given on the authority of such firm as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We have filed with the SEC a registration statement on Form S-1 (including exhibits, schedules, and amendments) under the Securities Act with respect to the shares of common stock offered by this prospectus. This prospectus does not contain all the information set forth in the registration statement. For further information about us and the shares of common stock to be sold in this offering, you should refer to the registration statement. Statements contained in this prospectus relating to the contents of any contract, agreement or other document are not necessarily complete and are qualified in all respects by the complete text of the applicable contract, agreement or other document, a copy of which has been filed as an exhibit to the registration statement. Whenever this prospectus refers to any contract, agreement, or other document, you should refer to the exhibits that are a part of the registration statement for a copy of the contract, agreement, or document.

We are subject to the reporting and information requirements of the Exchange Act and, as a result, file, or will file, periodic reports, proxy statements and other information with the SEC. These periodic reports and other information are available for inspection and copying at the SEC's public reference room and the website of the SEC, in each case, referred to below. We also maintain a website at http:// http://www.rhythmtx.com and make available free of charge through this website our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Exchange Act. We make these reports available through our website as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the SEC. The information contained on, or that can be accessed through, our website is not a part of this prospectus. The reference to our web address does not constitute incorporation by reference of the information contained in, or that can be accessed through, our website.

You may read and copy this information at the SEC's Public Reference Room at 100 F Street, N.E., Washington D.C. 20549, on official business days during the hours of 10:00 am to 3:00 pm. You may obtain information regarding the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC also maintains a website (http://www.sec.gov) that contains reports, proxy and information statements and other information regarding issuers that file electronically with the SEC.

RHYTHM PHARMACEUTICALS, INC.
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REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Stockholders and the Board of Directors of Rhythm Pharmaceuticals, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Rhythm Pharmaceuticals, Inc. (the Company) as of December 31, 2017 and 2016, the related consolidated statements of operations and comprehensive loss, convertible preferred stock and stockholders' equity (deficit) and cash flows for each of the three years in the period ended December 31, 2017, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2017 and 2016, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2017, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2015.
Boston, Massachusetts
March 12, 2018, except for Note 12, as to which the date is June 11, 2018

RHYTHM PHARMACEUTICALS, INC.

CONSOLIDATED BALANCE SHEETS

(in thousands, except share and per share data)

	December 31, 2017	December 31, 2016
Assets		
Current assets:		
Cash and cash equivalents	$ 34,236	$ 6,540
Short-term investments	113,846	3,997
Prepaid expenses and other current assets	2,589	638
Total current assets	150,671	11,175
Property, plant and equipment, net	840	930
Deferred issuance costs	—	9
Restricted cash	225	225
Total assets	$ 151,736	$ 12,339
Liabilities, convertible preferred stock and stockholders' equity (deficit)		
Current liabilities:		
Accounts payable	$ 2,427	$ 1,895
Due to related party	—	105
Deferred rent	83	76
Accrued expenses and other current liabilities	4,210	2,655
Total current liabilities	6,720	4,731
Long-term liabilities:		
Deferred rent	228	311
Total liabilities	6,948	5,042
Commitments and contingencies		
Preferred stock:		
Series A Convertible Preferred Stock, $0.001 par value: 10,000,000 shares authorized; no shares issued and outstanding at December 31, 2017 and 40,000,000 shares issued and outstanding at December 31, 2016; (aggregate liquidation preference of $0 and $44,129 at December 31, 2017 and December 31, 2016 respectively)	—	40,000
Stockholders' equity (deficit):		
Common stock, $0.001 par value: 120,000,000 shares authorized; 27,284,140 and 10,196,292 shares issued and outstanding and December 31, 2017 and December 31, 2016, respectively	27	10
Additional paid-in capital	255,013	43,830
Accumulated deficit	(110,252)	(76,543)
Total stockholders' equity (deficit)	144,788	(32,703)
Total liabilities, convertible preferred stock and stockholders' equity (deficit)	$ 151,736	$ 12,339

The accompanying notes are an integral part of these financial statements

RHYTHM PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS

(in thousands, except share and per share data)

	Year Ended December 31, 2017	Year Ended December 31, 2016	Year Ended December 31, 2015
Operating expenses:			
Research and development	$ 22,894	$ 19,594	$ 7,148
Selling, general, and administrative	9,518	6,311	3,425
Total operating expenses	32,412	25,905	10,573
Loss from operations	(32,412)	(25,905)	(10,573)
Other income (expense):			
Revaluation of Series A Investor Instrument and Series A Investor Right/Obligation	(1,863)	—	(500)
Interest income, net	566	33	—
Total other income (expense):	(1,297)	33	(500)
Net loss and comprehensive loss	$ (33,709)	$ (25,872)	$ (11,073)
Net loss attributable to common stockholders	$ (37,582)	$ (29,074)	$ (12,000)
Net loss attributable to common stockholders per common share, basic and diluted	$ (2.83)	$ (2.85)	$ (1.18)
Weighted average common shares outstanding, basic and diluted	13,267,960	10,196,292	10,196,292

The accompanying notes are an integral part of these financial statements

RHYTHM PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' EQUITY (DEFICIT)

(in thousands, except share and per share data)

	Series A Convertible Preferred Stock		Common Stock		Series A-1 Junior Preferred Stock		Additional Paid-In Capital	Accumulated Deficit	Total Stockholders' Equity (Deficit)
	Shares	Amount	Shares	Amount	Shares	Amount			
Balance at December 31, 2014	—	$ —	10,196,292	$ 10	—	$ —	$ 39,230	$ (39,598)	$ (358)
Equity contribution	—	—	—	—	—	—	2,094	—	2,094
Modification of warrant in connection with a license agreement	—	—	—	—	—	—	923	—	923
Stock compensation expense	—	—	—	—	—	—	298	—	298
Dividend to Rhythm Holding Company LLC (associated with common stock options granted to employees of Motus Therapeutics, Inc.)	—	—	—	—	—	—	2,695	—	2,695
Dividend to Rhythm Holding Company LLC (associated with common stock options granted to employees of Motus Therapeutics, Inc.)	—	—	—	—	—	—	(2,695)	—	(2,695)
Reclassification of Series A Investor Right/Obligation liability upon Series A second tranche closing	—	883	—	—	—	—	117	—	117
Issuance of Series A Convertible Preferred Stock	40,000,000	39,117	—	—	—	—	—	—	—
Net loss	—	—	—	—	—	—	—	(11,073)	(11,073)
Balance at December 31, 2015	40,000,000	40,000	10,196,292	10	—	—	42,662	(50,671)	(7,999)
Stock compensation expense	—	—	—	—	—	—	1,168	—	1,168
Net loss	—	—	—	—	—	—	—	(25,872)	(25,872)
Balance at December 31, 2016	40,000,000	40,000	10,196,292	10	—	—	43,830	(76,543)	(32,703)
Stock compensation expense	—	—	—	—	—	—	2,278	—	2,278
Issuance of common stock in connection with exercise of stock options	—	—	152,671	—	—	—	700	—	700
Change in unrealized loss on marketable securities	—	—	—	—	—	—	(141)	—	(141)
Issuance of Series A Convertible Preferred Stock	40,949,999	40,622	—	—	—	—	(108)	—	(108)
Settlement of Series A investor instrument	—	328	—	—	—	—	1,863	—	1,863
Exchange of common stock held by LLC entity for Series A-1 Junior Preferred Stock	—	—	(8,578,661)	(8)	78,666,209	79	(71)	—	—
Issuance of common stock upon completion of initial public offering, net of offering costs	—	—	8,107,500	8	—	—	125,650	—	125,658
Conversion of Series A Convertible Preferred Stock and Series A-1 Junior Preferred Stock into common stock on a 9.17 to 1 basis	(80,949,999)	(80,950)	17,406,338	17	(78,666,209)	(79)	81,012	—	80,950
Net loss	—	—	—	—	—	—	—	(33,709)	(33,709)
Balance at December 31, 2017	—	$ —	27,284,140	$ 27	—	$ —	$ 255,013	$ (110,252)	$ 144,788

The accompanying notes are an integral part of these financial statements

RHYTHM PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS

(in thousands, except share and per share data)

	Fiscal Year Ended December 31, 2017	2016	2015
Operating activities			
Net loss	$ (33,709)	$ (25,872)	$ (11,073)
Adjustments to reconcile net loss to cash used in operating activities:			
Stock-based compensation expense	2,278	1,168	298
Depreciation and amortization	223	144	—
Non-cash rent expense	(76)	11	—
Modification of warrant in connection with license agreement	—	—	923
Mark to market revaluation of Series A Investor Instrument and Series A Investor Right/Obligation	1,863	—	500
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	(1,889)	41	(581)
Deferred issuance costs	9	1,472	(1,481)
Tenant improvement allowance	—	376	—
Accounts payable, accrued expenses and other current liabilities	1,946	160	3,838
Deferred grant income	—	(249)	249
Due to related parties	(105)	(470)	575
Net cash used in operating activities	(29,460)	(23,219)	(6,752)
Investing activities			
Purchases of short-term investments	(126,917)	(15,222)	—
Maturities of short-term investments	17,006	11,169	—
Purchases of property, plant and equipment	(133)	(1,057)	(17)
Net cash used in investing activities	(110,044)	(5,110)	(17)
Financing activities			
Net proceeds from issuance of common stock	125,658	—	—
Net proceeds from issuance of Series A Convertible Preferred Stock	40,842	—	39,617
Equity Contribution	—	—	2,094
Proceeds from the exercise of stock options	700	—	—
Net cash provided by financing activities	167,200	—	41,711
Net increase (decrease) in cash, cash equivalents and restricted cash	27,696	(28,329)	34,942
Cash, cash equivalents and restricted cash at beginning of year	6,765	35,094	152
Cash, cash equivalents and restricted cash at end of year	$ 34,461	$ 6,765	$ 35,094

The accompanying notes are an integral part of these financial statements

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements

(In thousands, except share and per share information)

1. Nature of Business

Rhythm Pharmaceuticals, Inc. (the "Company"), is a biopharmaceutical company focused on the development and commercialization of peptide therapeutics for the treatment of genetic deficiencies that result in life-threatening metabolic disorders. The Company's lead product candidate is setmelanotide (RM-493), which is a potent, first-in-class, melanocortin-4, or MC4, receptor agonist for the treatment of rare genetic disorders of obesity caused by MC4 pathway deficiencies. The Company is currently evaluating setmelanotide for the treatment of six genetic disorders of obesity: pro-opiomelanocortin, or POMC, leptin receptor, or LepR, Bardet-Biedl syndrome, Alström syndrome, POMC heterozygous, and POMC epigenetic disorders.

Corporate Reorganization

The Company is a Delaware corporation organized in February 2013 under the name Rhythm Metabolic, Inc. Prior to the Company's organization and the Corporate Reorganization referred to below, the Company was part of Rhythm Pharmaceuticals, Inc. (the "Predecessor Company"), a Delaware corporation which was organized in November 2008 and which commenced active operations in 2010.

In March 2013, the Predecessor Company underwent a corporate reorganization, (the "Corporate Reorganization"), pursuant to which all of the outstanding equity securities of the Predecessor Company were exchanged for units of Rhythm Holding Company, LLC, a newly-organized limited liability company (the "LLC entity"). After the consummation of this exchange and as part of the Corporate Reorganization, the Predecessor Company contributed setmelanotide and the MC4R agonist program to the Company and distributed to the LLC entity all of the then issued and outstanding shares of the Company's stock. The result of the Corporate Reorganization was that the Company and the Predecessor Company became wholly-owned subsidiaries of the LLC entity and the two product candidates and related programs that were originally held by the Predecessor Company were separated, with relamorelin and the ghrelin agonist program being retained by the Predecessor Company and setmelanotide and the MC4R agonist program being held by the Company. The Predecessor Company, after consummation of the Corporate Reorganization, is referred to within these Notes to Financial Statements as the Relamorelin Company and/or Motus.

On October 13, 2015, the Relamorelin Company changed its name to Motus Therapeutics, Inc ("Motus") and the Company changed its name to Rhythm Pharmaceuticals, Inc. On December 15, 2016, Motus was sold to a large pharmaceutical company. On August 21, 2017, the LLC entity distributed to its members all of its shares of the Company (see Note 5 for further discussion).

Liquidity

The Company has incurred operating losses and negative cash flows from operations since inception, incurred a net loss of $33,709, $25,872 and $11,073 during the years ended December 31, 2017, 2016 and 2015, respectively, and has an accumulated deficit of $110,252 as of December 31, 2017. The Company has primarily funded these losses through capital contributions received from the LLC entity and the sale of preferred and common stock to outside investors. To date, the Company has no product revenue and management expects operating losses to continue for the foreseeable future. The Company has devoted substantially all of its resources to its drug development efforts, comprising research and development, manufacturing, conducting clinical trials for its product candidates, protecting its intellectual property and general and administrative functions relating to these operations. The future success of the Company is

1. Nature of Business (Continued)

dependent on its ability to develop its product candidates and ultimately upon its ability to attain profitable operations. At December 31, 2017, the Company had $148,082 of cash and cash equivalents and short-term investments on hand. In the future, the Company will be dependent on obtaining funding from third parties, such as proceeds from the issuance of debt, sale of equity, and funded research and development programs, to maintain the Company's operations and meet the Company's obligations. There is no guarantee that additional equity or other financings will be available to the Company on acceptable terms, or at all. If the Company fails to obtain additional funding when needed, the Company would be forced to scale back, terminate its operations or seek to merge with or be acquired by another company. Management believes that the Company's existing cash resources will be sufficient to fund the Company's operating plan into the second half of 2019.

2. Summary of Significant Accounting Policies

Basis of Presentation

The Company's consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States ("GAAP"). Any reference in these notes to applicable guidance is meant to refer to the authoritative United States generally accepted accounting principles as found in the Accounting Standards Codification ("ASC") and Accounting Standards Updates ("ASU") of the Financial Accounting Standards Board ("FASB").

The Company has historically existed and functioned as part of the consolidated businesses of the Predecessor Company. As noted above, the Predecessor Company's setmelanotide and the MC4R agonist program were transferred to the Company as part of the Corporate Reorganization on March 21, 2013. These financial statements include the results of operations of setmelanotide and the MC4R agonist program from its inception. As part of the Corporate Reorganization, the Company also entered into a formal payroll services intercompany agreement with the Relamorelin Company. On November 16, 2016, the employees of the Relamorelin Company that were providing services to the Company, terminated their employment contracts with the Relamorelin Company and entered into new employment agreements with the Company. On December 15, 2016, the Relamorelin Company closed on its sale to a large pharmaceutical company. During 2016 and 2015, costs have been allocated to the Company for the purposes of preparing the financial statements based on a specific identification basis or, when specific identification is not practicable, a proportional cost allocation method which allocates expenses based upon the percentage of employee time and research and development effort expended on the Company's business as compared to total employee time and research and development effort of the combined Motus and Rhythm. The proportional use basis adopted to allocate shared costs is in accordance with the guidance of SEC Staff Accounting Bulletin ("SAB") Topic 1B, *Allocation Of Expenses And Related Disclosure In Financial Statements Of Subsidiaries*, *Divisions Or Lesser Business Components Of Another Entity*. Management has determined that the method of allocating costs to the Company is reasonable. Cost allocation was no longer required subsequent to the 2016 sale of the Relamorelin Company.

Management believes that the statements of operations include a reasonable allocation of costs and expenses incurred by the Relamorelin Company, which benefited the Company. However, such amounts may not be indicative of the actual level of costs and expenses that would have been incurred by the Company if it had operated as an independent company or of the costs and expenses expected to be incurred in the future. Management has not presented an estimate of what the expenses of the Company

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

2. Summary of Significant Accounting Policies (Continued)

would have been on a standalone basis as it was not practicable to make a reasonable estimate. As such, the financial information herein may not necessarily reflect the financial position, results of operations and cash flows of the Company expected in the future or what it would have been had it been an independent company during the periods presented.

As described above, Relamorelin Company employee costs are allocated to the Company based on a proportional use method. For those employees who became employees of the Company on November 16, 2016, their full employment cost was $2,727 and $3,155 for the years ended December 31, 2016 and 2015, respectively.

On September 22, 2017, the Company's board of directors approved a 1-for-9.17 reverse stock split of the Company's issued and outstanding shares of common stock. All share and per share amounts in the financial statements have been retrospectively adjusted for all periods presented to give effect of the reverse stock split.

On October 5, 2017, the Company filed an amended and restated certificate of incorporation with the Secretary of State of the State of Delaware to increase its authorized number of shares of common stock to 120,000,000 shares of common stock, $0.001 par value per share and 10,000,000 shares of preferred stock, $0.001 par value per share.

On October 10, 2017 the Company completed its initial public offering ("IPO") of 8,107,500 shares of common stock at an offering price of $17.00 per share, which included the exercise in full by the underwriters of their option to purchase up to 1,057,500 additional shares of common stock. The Company received gross proceeds of approximately $137,828 or net proceeds of $125,658 after deducting underwriting discounts, commissions and estimated offering expenses. In connection with the IPO, the Company's outstanding shares of convertible preferred stock were automatically converted into 17,406,338 shares of common stock. After the IPO and as of December 31, 2017, our outstanding common shares were 27,284,140.

Use of Estimates

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent liabilities at the date of the financial statements and the reported amounts of revenue and expenses during the reporting period. The Company bases its estimates on historical experience and other market-specific or other relevant assumptions that it believes to be reasonable under the circumstances. This process may result in actual results differing materially from those estimated amounts used in the preparation of the financial statements if these results differ from historical experience, or other assumptions do not turn out to be substantially accurate, even if such assumptions are reasonable when made. Significant estimates relied upon in preparing these financial statements include the allocation of costs from the Relamorelin Company in accordance with SAB Topic 1B, accrued expenses, stock-based compensation expense, the valuation allowance on the Company's deferred tax assets, and the fair value of the Series A Investor Instrument. See Note 4.

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

2. Summary of Significant Accounting Policies (Continued)

Principles of Consolidation

The consolidated financial statements include the accounts of Rhythm Pharmaceuticals, Inc. and its subsidiaries. All significant intercompany balances and transactions have been eliminated in consolidation.

Off-Balance Sheet Risk and Concentrations of Credit Risk

Financial instruments, which potentially subject the Company to significant concentration of credit risk, consist primarily of cash and cash equivalents and short-term investments, which are maintained at two federally insured financial institutions. The deposits held at these two institutions are in excess of federally insured limits. The Company has not experienced any losses in such accounts and management believes that the Company is not exposed to significant credit risk due to the financial position of the depository institutions in which those deposits are held. The Company has no off-balance sheet risk, such as foreign exchange contracts, option contracts, or other foreign hedging arrangements.

Segment Information

Operating segments are defined as components of an entity about which separate discrete information is available for evaluation by the chief operating decision maker, or decision-making group, in deciding how to allocate resources and in assessing performance. The Company views its operations and manages its business in one operating segment operating exclusively in the United States.

Cash and Cash Equivalents

The Company considers all highly liquid investments with original or remaining maturity from the date of purchase of three months or less to be cash equivalents. Cash and cash equivalents includes bank demand deposits, U.S. treasury bills and money market funds that invest primarily in U.S. government treasuries.

Short-term Investments

Short-term investments consist of investments with original maturities greater than 90 days, as of the date of purchase. The Company has classified its investments with maturities beyond one year as short term, based on their highly liquid nature and because such marketable securities represent the investment of cash that is available for current operations. The Company considers its investment portfolio available-for-sale. Accordingly, these investments are recorded at fair value, which is based on quoted market prices. Unrealized gains and losses are reported as a component of accumulated other comprehensive income (loss) in stockholders' equity (deficit). Realized gains and losses and declines in value judged to be other than temporary are included as a component of other income (expense), net based on the specific identification method. When determining whether a decline in value is other than temporary, the Company considers various factors, including whether the Company has the intent to sell the security, and whether it is more likely than not that the Company will be required to sell the security prior to recovery of its amortized cost basis. Fair value is determined based on quoted market prices.

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

2. Summary of Significant Accounting Policies (Continued)

Restricted Cash

Restricted cash consists of a security deposit in the form of a letter of credit placed in a separate restricted bank account as required under the terms of the Company's new lease arrangement for its corporate office in Boston, Massachusetts.

Deferred Issuance Costs

Deferred issuance costs, which consist of direct incremental legal and accounting fees relating to the IPO, were capitalized and included in non-current assets. The deferred issuance costs were to be offset against IPO proceeds upon the consummation of the offering. In the event the offering was terminated, deferred issuance costs would be expensed.

The Company had capitalized $1,825 of deferred issuance costs related to a prior registration statement confidentially submitted to the Securities and Exchange Commission in 2015 and 2016. In the fourth quarter of 2016, the Company wrote off these deferred issuance costs to general and administrative expenses because the offering was postponed significantly in excess of 90 days. As a result, the costs were not deemed realizable as the Company incurred similar costs in connection with its IPO in October 2017. The Company incurred $9 of deferred issuance costs as of December 31, 2016, which is included in non-current assets.

Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets consist primarily of costs incurred in advance of services being received, including services related to clinical trial programs.

	December 31,	
	2017	2016
Prepaid research and development costs	$ 1,533	$ 422
Other current assets	1,056	216
Prepaid expenses and other current assets	$ 2,589	$ 638

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

2. Summary of Significant Accounting Policies (Continued)

Property, Plant and Equipment

Property, Plant and Equipment consists of the following:

	Useful Life	December 31, 2017	December 31, 2016
Leasehold improvements	*	$ 891	$ 891
Office equipment	5 years	70	70
Computers and software	3 years	19	19
Furniture and fixtures	5 years	227	94
		1,207	1,074
Less accumulated depreciation and amortization		(367)	(144)
Property, Plant and Equipment, net		$ 840	$ 930

* Shorter of asset life or lease term.

2017 Series A Investor Instrument, 2015 Series A Investor Right/Obligation and 2015 Series A Investor Call Option

The Company classified its 2017 Series A Investor Instrument, 2015 Series A Investor Right/Obligation and its 2015 Series A Investor Call Option (See Notes 4 and 5) as a liability as it is a free-standing financial instrument. The 2017 Series A Investor Instrument, the 2015 Series A Investor Right/Obligation and the 2015 Series A Investor Call Option were recorded at fair value upon the issuance of the Company's series A preferred stock in January 2017 and August 2015, respectively, and subsequently remeasured to fair value at each reporting period. Changes in fair value of these financial instruments are recognized as a component of other income (expense), net in the statement of operations and comprehensive loss.

The fair value of the 2017 Series A Investor Instrument is determined to be the sum of the fair values of the 2017 Series A Investor Right/Obligation and the 2017 Investor Call Option. The Company estimated the fair value of the 2017 and 2015 Series A Investor Right/Obligations as the probability-weighted present value of the expected benefit of the investment.

The Company used the Black-Scholes option-pricing model, which incorporates assumptions and estimates, to value the 2017 and 2015 Series A Investor Call Options and assessed these assumptions and estimates on a quarterly basis as additional information impacting the assumptions was obtained. Estimates and assumptions impacting the fair value measurement include the fair value per share of the underlying series A preferred stock, the expected term of the Series A Investor Call Options, risk-free interest rate, expected dividend yield and expected volatility of the price of the underlying preferred stock. The Company determined the fair value per share of the underlying preferred stock by taking into consideration the most recent sale of its convertible preferred stock and the investors' right to invest in a subsequent tranche. As the Company was a private company and lacked company-specific historical and implied volatility information of its stock, it estimated its expected stock volatility based on the historical volatility of publicly traded peer companies for a term comparable to the estimated term of the Series A

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

2. Summary of Significant Accounting Policies (Continued)

Investor Call Options. The risk-free interest rate was determined by reference to the U.S. Treasury yield curve for time periods approximately equal to the estimated term of the Series A Investor Call Options. A dividend yield of zero was assumed.

Government Grants

The Company obtained an Orphan Products Development grant entitled "Phase 2 study of the melanocortin 4 receptor agonist RM-493 for the treatment of Prader-Willi syndrome" in 36 patients. The grant was awarded by the Public Health Service ("PHS") Food and Drug Administration. The PHS grant is for a total of $999 and is effective July 2015 through June 2018 for reimbursement of expenses relating to the Phase 2 Prader-Willi Study.

The Company recognizes government grants upon the determination that it will comply with the conditions attached to the grant arrangement and the grant will be received. Government grants are recognized in the statements of operations on a systematic basis over the periods in which the Company recognizes the related costs for which the government grant is intended to compensate. Government grants for research and development efforts are deducted in reporting the related expense in the statement of operations. Government grant income received during the year ended December 31, 2017, 2016 and 2015 of zero, $642 and $147, respectively, and is included as a deduction to research and development expense in the consolidated statements of operations.

Research and Development Expenses

Costs incurred in the research and development of the Company's products are expensed to operations as incurred. Research and development expenses consist of costs incurred in performing research and development activities, including salaries and benefits, facilities costs, overhead costs, contract services and other outside costs, both directly incurred and allocated from the Relamorelin Company. The value of goods and services received from contract research organizations or contract manufacturing organizations in the reporting period are estimated based on the level of services performed and progress in the period for which the Company has not yet received an invoice from the supplier.

Nonrefundable advance payments for goods or services to be received in the future for use in research and development activities are recorded as prepaid expenses, and expensed as the related goods are delivered or the services are performed.

Income Taxes

The Company is taxed as a C corporation for federal income tax purposes. Income taxes for the Company are recorded in accordance with FASB ASC Topic 740, *Income Taxes* ("ASC 740"), which provides for deferred taxes using an asset and liability approach. Income taxes have been calculated on a separate tax return basis. Certain of the Company's activities and costs have been included in the tax returns filed by the Relamorelin Company and the LLC entity. Prior to the Corporate Reorganization, the Company's operations were included in the tax returns filed by the Predecessor Company. The Company has filed tax returns on its own behalf since the Corporate Reorganization.

The Company accounts for income taxes under the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

2. Summary of Significant Accounting Policies (Continued)

have been included in the financial statements. Under this method, the Company determined deferred tax assets and liabilities on the basis of the differences between the financial statement and tax bases of assets and liabilities by using enacted tax rates in effect for the year in which the differences are expected to reverse. The effect of a change in tax rates on deferred tax assets and liabilities is recognized in income in the period that includes the enactment date. The Company recognized deferred tax assets to the extent that it believes that these assets are more likely than not to be realized. In making such a determination, the Company considers all available positive and negative evidence, including future reversals of existing taxable temporary differences, projected future taxable income, tax-planning strategies, and results of recent operations. If the Company determines that it would be able to realize our deferred tax assets in the future in excess of their net recorded amount, it would make an adjustment to the deferred tax asset valuation allowance, which would reduce the provision for income taxes.

The Company records uncertain tax positions in accordance with ASC 740 on the basis of a two-step process in which (1) it determines whether it is more likely than not that the tax positions will be sustained on the basis of the technical merits of the position and (2) for those tax positions that meet the more-likely-than-not recognition threshold, the Company recognizes the largest amount of tax benefit that is more than 50 percent likely to be realized upon ultimate settlement with the related tax authority.

The Company recognizes interest and penalties related to unrecognized tax benefits on the income tax expense line in the accompanying consolidated statement of operations. As of December 31, 2017, no accrued interest or penalties are included on the related tax liability line in the consolidated balance sheet.

Net Loss Per Share Attributable to Common Shareholders

Basic net loss per share attributable to common stockholders is calculated by dividing net loss attributable to common stockholders by the weighted average shares outstanding during the period, without consideration for Common Stock equivalents. Net loss attributable to common stockholders is calculated by adjusting the net loss of the Company for cumulative preferred stock dividends. During periods of income, the Company allocates participating securities a proportional share of income determined by dividing total weighted average participating securities by the sum of the total weighted average common shares and participating securities (the "two class method"). The Company's convertible preferred stock participates in any dividends declared by the Company and are therefore considered to be participating securities. Participating securities have the effect of diluting both basic and diluted earnings per share during periods of income. During periods of loss, the Company allocates no loss to participating securities because they have no contractual obligation to share in the losses of the Company. Diluted net loss per share attributable to common stockholders is calculated by adjusting weighted average shares outstanding for the dilutive effect of Common Stock equivalents outstanding for the period, determined using the treasury-stock and if-converted methods. For purposes of the diluted net loss per share attributable to common stockholders calculation, convertible preferred stock and stock options are considered to be Common Stock equivalents but have been excluded from the calculation of diluted net loss per share attributable to common stockholders, as their effect would be anti-dilutive for all periods presented. Therefore, basic and diluted net loss per share were the same for all periods presented.

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

2. Summary of Significant Accounting Policies (Continued)

Basic and diluted earnings per share is calculated as follows:

	Year Ended December 31,		
	2017	2016	2015
Numerator:			
Net loss	$ (33,709)	$ (25,872)	$ (11,073)
Cumulative dividends on convertible preferred shares	(3,873)	(3,202)	(927)
Loss attributable to common shares—basic and diluted	$ (37,582)	$ (29,074)	$ (12,000)
Denominator:			
Weighted-average number of common shares—basic and diluted	13,267,960	10,196,292	10,196,292
Loss per common share—basic and diluted	$ (2.83)	$ (2.85)	$ (1.18)

Patent Costs

Costs to secure and defend patents are expensed as incurred and are classified as general and administrative expenses. Patent costs were $180, $231 and $280 for the years ended December 31, 2017, 2016 and 2015, respectively.

Subsequent Events

The Company considers events or transactions that occur after the balance sheet date but prior to the issuance of the financial statements to provide additional evidence for certain estimates or to identify matters that require additional disclosure. Subsequent events have been evaluated as required.

Application of New or Revised Accounting Standards

From time to time, new accounting pronouncements are issued by the FASB and adopted by the Company as of the specified effective date. Unless otherwise discussed, the Company believes that the impact of recently issued standards that are not yet effective will not have a material impact on its financial position or results of operations upon adoption.

In April 2012, the Jump-Start Our Business Startups Act (the "JOBS Act") was signed into law. The JOBS Act contains provisions that, among other things, reduce certain reporting requirements for an "emerging growth company." As an emerging growth company, the Company elected to not take advantage of the extended transition period afforded by the JOBS Act for the implementation of new or revised accounting standards, and as a result, will comply with new or revised accounting standards on the relevant dates on which adoption of such standards is required for non-emerging growth companies.

In February 2016, the FASB issued ASU 2016-02, Leases (Topic 842). ASU 2016-02 requires lessees to recognize lease assets and lease liabilities for those leases classified as operating leases under previous GAAP. A lessee should recognize in the statement of financial position a liability to make lease payments

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

2. Summary of Significant Accounting Policies (Continued)

(the lease liability) and a right-of-use asset representing its right to use the underlying asset for the lease term. For leases with a term of 12 months or less, a lessee is permitted to make an accounting policy election by class of underlying asset not to recognize lease assets and lease liabilities. The recognition, measurement, and presentation of expenses and cash flows arising from a lease by a lessee have not significantly changed from previous GAAP. There continues to be a differentiation between finance leases and operating leases. ASU 2016-02 is effective for fiscal years beginning after December 15, 2018, and interim periods within those fiscal years, and early adoption is permitted. The Company is currently in the process of evaluating the impact of adoption of ASU No. 2016-02 on its financial position and results of operations.

In March 2016, the FASB issued ASU 2016-09, *Improvements to Employee Share-Based Payment Accounting (Topic 718)* that changes the accounting for certain aspects of share-based payments to employees. The guidance requires the recognition of the income tax effects of awards in the income statement when the awards vest or are settled, thus eliminating additional paid in capital pools. The guidance also allows for the employer to repurchase more of an employee's shares for tax withholding purposes without triggering liability accounting. In addition, the guidance allows for a policy election to account for forfeitures as they occur rather than on an estimated basis. The guidance is effective for annual periods beginning after December 15, 2016, and interim periods within those annual periods with early adoption permitted. Accordingly, the standard is effective for the Company on January 1, 2018. The Company adopted the standard as of January 1, 2017. The adoption did not have a material impact on the Company's financial position, results of operations or cash flows.

In May 2017, the FASB issued ASU 2017-09, Compensation—Stock Compensation (Topic 718): Scope of Modification Accounting, ("ASU 2017-09"). ASU 2017-09 provides clarity and reduces both (1) diversity in practice and (2) cost and complexity when applying the guidance in Topic 718, to a change to the terms or conditions of a share-based payment award. The amendments in ASU 2017-09 should be applied prospectively to an award modified on or after the adoption date. This ASU is effective for fiscal years, and interim periods within those years, beginning after December 15, 2017. The adoption of this ASU is not expected to have a material impact on the Company's financial position or results of operations.

In July 2017, the FASB issued ASU 2017-11, Earnings Per Share (Topic 260), Distinguishing Liabilities from Equity (Topic 480) and Derivatives and Hedging (Topic 815): I. Accounting for Certain Financial Instruments with Down Round Features; II. Replacement of the Indefinite Deferral for Mandatorily Redeemable Financial Instruments of Certain Nonpublic Entities and Certain Mandatorily Redeemable Noncontrolling Interests with a Scope Exception, ('ASU 2017-11'). Part I of this update addresses the complexity of accounting for certain financial instruments with down round features. Down round features are features of certain equity-linked instruments (or embedded features) that result in the strike price being reduced on the basis of the pricing of future equity offerings. Current accounting guidance creates cost and complexity for entities that issue financial instruments (such as warrants and convertible instruments) with down round features that require fair value measurement of the entire instrument or conversion option. Part II of this update addresses the difficulty of navigating Topic 480, Distinguishing Liabilities from Equity, because of the existence of extensive pending content in the FASB Accounting Standards Codification. This pending content is the result of the indefinite deferral of accounting requirements about mandatorily redeemable financial instruments of certain nonpublic entities and certain mandatorily redeemable noncontrolling interests. The amendments in Part II of this update do not have an

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

2. Summary of Significant Accounting Policies (Continued)

accounting effect. This ASU is effective for fiscal years, and interim periods within those years, beginning after December 15, 2018. The Company is currently assessing the potential impact of adopting ASU 2017-11 on its financial statements and related disclosures.

3. Accrued Expenses

Accrued expenses consisted of the following:

	December 31, 2017	December 31, 2016
Research and development costs	$ 2,771	$ 2,049
Professional fees	327	182
Payroll related	1,094	344
Other	18	80
Accrued expenses	$ 4,210	$ 2,655

4. Fair Value of Financial Assets and Liability

As of December 31, 2017 and 2016, the carrying amount of cash and cash equivalents and short-term investments was $148,082 and $10,537, respectively, which approximates fair value. Cash and cash equivalents and short-term investments includes investments in money market funds that invest in U.S. government securities that are valued using quoted market prices. Accordingly, money market funds and government funds are categorized as Level 1 and had a total balance of $34,698 and $7,984 as of December 31, 2017 and 2016, respectively. The financial assets valued based on level 2 inputs consist of corporate debt securities, which consist of investments in highly-rated investment-grade corporations.

A financial liability was recognized by the Company during the year ending December 31, 2017 related to the 2017 Series A Investor Instrument. The liability was valued based on significant inputs not observable in the market, which represents a Level 3 measurement within the fair value hierarchy. Upon the closing of the second tranche of the 2017 Series A preferred financing in August 2017, this liability was settled. For the year ended December 31, 2016, the Company had no financial liability outstanding measured at fair value. The Company recognized a financial liability during 2015 related to its 2015 Series A Investor Right/Obligation and 2015 Series A Investor Call Option that was exercised or expired, respectively, in December 2015. The liability was based on significant inputs not observable in the market, which represents a Level 3 measurement within the fair value hierarchy.

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

4. Fair Value of Financial Assets and Liability (Continued)

The following tables present information about the Company's financial assets and liabilities measured at fair value on a recurring basis and indicate the level of the fair value hierarchy utilized to determine such fair values:

	Fair value Measurements as of December 31, 2017 using:			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash Equivalents:				
Corporate Debt Securities	$ —	$ 15,104	$ —	$ 15,104
Money Market Funds	17,753	—	—	17,753
Marketable Securities:				
Corporate Debt Securities	—	96,901	—	96,901
U.S. Treasury Securities	16,945	—	—	16,945
Total	$ 34,698	$ 112,005	$ —	$ 146,703
Liabilities:				
2017 Series A Investor Instrument	$ —	$ —	$ —	$ —
Total	$ —	$ —	$ —	$ —

	Fair value Measurements as of December 31, 2016 using:			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash Equivalents:				
Government Funds	$ 2,000	$ —	$ —	$ 2,000
Money Market Funds	1,987	—	—	1,987
Marketable Securities:				
Government Funds	3,997	—	—	3,997
Total	$ 7,984	$ —	$ —	$ 7,984

Marketable Securities

The following tables summarize the Company's marketable securities:

	December 31, 2017			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Assets				
Corporate Debt Securities (due within 1 year)	$ 97,029	$ —	$ (128)	$ 96,901
U.S. Treasury Securities (due within 1 year)	16,958	—	(13)	16,945
	$ 113,987	$ —	$ (141)	$ 113,846

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

4. Fair Value of Financial Assets and Liability (Continued)

	December 31, 2016			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Assets				
Government Funds (due within 1 year)	$ 3,997	$ —	$ —	$ 3,997
	$ 3,997	$ —	$ —	$ 3,997

Below is a roll forward of the fair value of the financial liability, the 2017 Series A Investor Instrument for the year ended December 31, 2017:

	2017 Series A Investor Instrument
Fair value at December 31, 2016	$ —
Fair value upon the January 2017 Initial Closing, net	328
Change in fair value through the date of settlement	1,863
Reclassification of liability upon August 2017 Second Tranche Closing	(2,191)
Fair value at December 31, 2017	$ —

The fair value of the Series A Investor Instrument is the sum of the probability-weighted fair value of the 2017 Investor Right/Obligation and the 2017 Series A Call Option.

The following assumptions and inputs were used in determining the fair value of the 2017 Series A Investor Call Option valued using the Black- Scholes option pricing model:

	August 2017 Second Tranche Closing
Series A Convertible Preferred Stock Exercise Price	$ 1.00
Series A Convertible Preferred Stock Fair Value	$ 1.33
Expected term	1.5 months
Expected volatility	64.0%
Expected interest rate	0.95%
Expected dividend yield	—

The Company estimated the fair value of the 2017 Series A Investor Right/Obligation as the probability-weighted present value of the expected benefit of the investment. The expected benefit is the difference between the expected future value of shares issued upon the second tranche closing and the investment price for the second tranche closing. The expected future value is estimated as a weighted average of IPO and remain private scenarios, and the future value is converted to a present value assuming a closing date of August 15, 2017 and a nominal, risk-free discount rate.

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

4. Fair Value of Financial Assets and Liability (Continued)

Below is a roll forward of the fair value of financial liabilities for the year ended December 31, 2015:

	2015 Series A Investor Right/Obligation And 2015 Series A Investor Call Option
Fair value at December 31, 2014	$ —
Fair value upon the August 2015 Initial Closing	500
Change in fair value through the date of settlement	500
Reclassification of liability upon December 2015 Second Tranche closing	(1,000)
Fair value at December 31, 2015	$ —

The following assumptions and inputs were used in determining the fair value of the 2015 Series A Investor Call Option valued using the Black- Scholes option pricing model:

	August 2015 Initial Tranche Closing
Series A Convertible Preferred Stock Exercise Price	$ 1.00
Series A Convertible Preferred Stock Fair Value	$ 0.81
Expected term	2 months
Expected volatility	24.0%
Expected interest rate	0.08%
Expected dividend yield	—

The 2015 Series A Investor Call Option expired upon the Second Tranche Closing in December 2015.

The Company estimated the fair value of the 2015 Series A Investor Right/Obligation as the probability-weighted present value of the expected benefit of the investment. The expected benefit is the difference between the expected future value of shares issued upon the second tranche closing and the investment price for the second tranche closing. The expected future value as of the August 2015 Initial Tranche Closing was estimated through a backsolve calculation which assumes a 70 percent probability of closing, a discount rate of 0.08% and a second tranche closing date of November 30, 2015.

The Company performed a contemporaneous valuation of the 2015 Series A Investor Right/Obligation to invest in the second tranche of our series A preferred stock financing. This valuation coincided with the 2015 Series A Second Tranche Closing on December 1, 2015. The Company valued the 2015 Series A Investor Right/Obligation as the benefit associated with the second tranche investment. The benefit is a function of the difference between the fair value of the series A shares and the 2015 Series A Investor Right/Obligation exercise price on the date of closing and the number of shares acquired. The Company estimated the fair value of the 2015 Series A Investor Right/Obligation as the probability weighted average of two scenarios: an IPO and a remain-private scenario.

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

5. Preferred Stock

In August 2015, pursuant to the Series A Preferred Stock Purchase Agreement, by and among the Company and certain purchasers, and as part of an initial tranche closing, the Company issued 25,000,000 shares of Series A Convertible Preferred Stock, par value $0.001 per share, at a purchase price of $1.00 per share, resulting in net proceeds of $24,976 to the Company (the "August 2015 Initial Tranche Closing"). The Series A Preferred Stock Purchase Agreement provided for the delayed issuance of up to an additional 15,000,000 shares of Series A Convertible Preferred Stock as part of a Second Tranche Closing. The delayed issuance was to be automatically settled upon the achievement of a specific milestone, resulting in the issuance of shares of Series A Convertible Preferred Stock (the "2015 Series A Investor Right/Obligation"). The 2015 Series A Investor Call Option would become exercisable in the event that a Second Tranche Closing was not been consummated. Both the 2015 Series A Investor Right/Obligation and the 2015 Series A Investor Call Option were evaluated and determined to be free standing instruments and were being accounted as liabilities (see Note 2). In December 2015, the specific milestones were met and 15,000,000 shares of Series A Convertible Preferred Stock were issued at a purchase price of $1.00 per share for net proceeds of $14,641. The 2015 Series A Investor Call Option expired unexercised at that time.

In January 2017, pursuant to the Series A preferred stock purchase agreement, by and among the Company and certain purchasers, and as part of an initial tranche closing, the Company issued 20,475,001 shares of Series A convertible preferred stock, par value $0.001 per share, at a purchase price of $1.00 per share, resulting in net proceeds of $20,377 to the Company (the "January 2017 Initial Tranche Closing"). The Series A preferred stock purchase agreement provided for the delayed issuance by the Company of up to an additional 20,474,998 shares of Series A convertible preferred stock as part of a second tranche closing at a purchase price of $1.00 per share (the "2017 Series A Investor Right/Obligation"). The second tranche is contingent upon: (1) the Company's cash, cash equivalents and short-term investments balance, net of accounts payable and accrued liabilities, falling below $5.0 million and (2) the Company's satisfaction of contractual and customary representations and warranties. Unless otherwise mutually agreed upon in writing, the rights and obligations underlying the second tranche (if not previously executed) will terminate on the first to occur of the following dates: (1) the date (the "Roadshow Acceleration Date") on which the Company files with the U.S. Securities and Exchange Commission, or SEC, the last pre-effective amendment to the registration statement prior to the start of the Company's roadshow in connection with the IPO, provided, that such termination shall be contingent upon the consummation of the IPO pursuant to the same registration statement that was on file with the SEC on the Roadshow Acceleration Date, without withdrawal thereof or filing of a subsequent registration statement in replacement thereof; and (2) the date of the consummation of a Deemed Liquidation Event (as defined below). To the extent the closing of the second tranche has not already taken place, the investors in the first tranche also have a call right on the shares underlying the second tranche whereby such shares can be purchased for the same price as the second tranche (the "2017 Series A Investor Call Option"). The 2017 Series A Investor Call Option terminates upon the Roadshow Acceleration Date. The 2017 Series A Investor Right/Obligation and the 2017 Series A Investor Call Option have been evaluated and determined to be a free standing instrument, the 2017 Series A Investor Instrument. The 2017 Series A Investor Instrument was accounted for as a liability (see Note 2).

In August 2017, the Series A Investors waived the $5.0 million cash balance requirement of the Series A Investor Right/Obligation and closed the second tranche of the series A preferred stock financing. The Company issued 20,474,998 shares of Series A convertible preferred stock, par value $0.001 per share,

5. Preferred Stock (Continued)

at a purchase price of $1.00 per share, resulting in gross proceeds of $20,475 to the Company. The 2017 Series A Investor Call Option expired unexercised at that time.

Upon the closing of the IPO, the Series A convertible preferred stock automatically converted into shares of common stock on a 9.17-for-1 basis.

The holders of the Series A convertible preferred stock had the following rights and preferences:

Voting Rights

The holders of Series A convertible preferred stock are entitled to vote, together with the holders of common stock, on all matters submitted to stockholders for a vote. Each preferred stockholder is entitled to the number of votes equal to the number of shares of common stock into which each preferred share is convertible at the time of such vote. In addition, pursuant to the Company's charter, the holders of record of the outstanding shares of Series A convertible preferred stock are entitled to elect one director to serve as the Series A preferred director on the board of directors of the Company.

Dividends

The holders of Series A convertible preferred stock are entitled to receive dividends in preference to any dividend on common stock at the rate of 8.0% per year of the original issue price. Dividends shall accrue annually, whether or not declared, and shall be cumulative. The Company may not declare, pay or set aside any dividends on shares of any other class or series of capital stock of the Company unless the holders of Series A convertible preferred stock then outstanding shall first receive, or simultaneously receive, dividends on each outstanding share of Series A convertible preferred stock. Through December 31, 2017, no dividends had been declared or paid by the Company. Accrued dividends, whether or not declared, shall also be payable upon any liquidation event. At December 31, 2017 and December 31, 2016, cumulative preference dividends amounted to zero, or $0.00 per share and $4,129, or $0.10 per share, respectively.

Liquidation

In the event of any liquidation, dissolution or winding-up of the Company or a Deemed Liquidation Event (as defined below), the holders of Series A convertible preferred stock then outstanding shall be entitled to be paid out of the assets of the Company available for distribution to stockholders, and before any payment shall be made to holders of common stock, an amount per share equal to greater of (i) the original issue price per share, plus any accrued but unpaid dividends thereon, whether or not declared, plus any declared but unpaid dividends thereon, if any, or (ii) such amount per share as would have been payable had all shares of Series A convertible preferred stock been converted to common stock prior to such liquidation. If upon such event, the assets of the Company available for distribution are insufficient to permit payment in full to the holders of Series A convertible preferred stock, the proceeds will be ratably distributed among the holders of Series A convertible preferred stock in proportion to the respective amounts that they would have received if they were paid in full. After payments have been made in full to the holders of Series A convertible preferred stock, the remaining assets of the Company available for distribution will be distributed among the holders of Series A convertible preferred stock, the holders of the Series A-1 convertible junior preferred stock, and the holders of common stock as if the shares of

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

5. Preferred Stock (Continued)

Series A convertible preferred stock and Series A-1 convertible junior preferred stock were converted to common stock immediately prior to the liquidation event.

A merger, acquisition, sale of voting control or other transaction of the Company in which the stockholders of the Company do not own a majority of the outstanding shares of the surviving company shall be considered a Deemed Liquidation Event. A sale, exclusive license, transfer or other disposition of all or substantially all of the assets of the Company shall also be considered a Deemed Liquidation Event. Each share of Series A convertible preferred stock may be redeemed at the option of the holder upon the occurrence of a deemed liquidation event. As of December 31, 2017 and December 31, 2016, the liquidation preference of the outstanding shares of Series A convertible preferred stock was approximately zero and $44,129, respectively.

Conversion

Each share of Series A convertible preferred stock is convertible into common stock at the option of the stockholder at any time after the date of issuance. In addition, each share of Series A convertible preferred stock will be automatically converted into shares of common stock, at the applicable conversion ratio then in effect, upon the earlier of (i) a qualified public offering with gross proceeds of at least $50,000 and a price of not less than $1.00 per share, subject to appropriate adjustment for any stock dividend, stock split, combination or other similar recapitalization, and (ii) the date specified by vote or written consent of the holders of at least two-thirds of the then outstanding shares of series A preferred stock. The shares of Series A convertible preferred stock will be converted to common stock, at par value, with the remainder recorded to additional paid-in capital.

The conversion ratio of the Series A convertible preferred stock is determined by dividing the original issue price per share by the conversion price of $9.17 per share, subject to appropriate adjustment in the event of any stock dividend, stock split, combination or recapitalization affecting the Series A convertible preferred stock.

On October 10, 2017 the Company completed its IPO and in connection with the IPO, the Company's outstanding shares of Series A convertible preferred stock and Series A-1 convertible junior preferred stock were automatically converted into 17,406,338 shares of common stock.

6. Common Stock

In March 2013, the Company issued 10,196,292 shares of common stock at a purchase price of $0.001 per share. As of December 31, 2016, the LLC entity owned all of these shares.

On August 21, 2017, the LLC entity exchanged 8,578,646 of its shares of the Company's common stock for 78,666,209 shares of the Company's series A-1 junior preferred stock and the LLC entity distributed all of its shares of the Company's series A-1 junior preferred stock to the holders of its preferred units and the remaining 1,617,646 shares of its common stock to the holders of its common units. Following this distribution, the LLC entity no longer owned any of the Company's shares. The series A-1 junior preferred stock is not redeemable and does not have a stated dividend or liquidation preference. These shares converted to common stock on a 9.17-to-1 basis upon the closing of the IPO in October 2017.

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

6. Common Stock (Continued)

In September 2017, the Company's board of directors approved a 1-for-9.17 reverse stock split of the Company's issued and outstanding shares of common stock. All shares and per share amounts in the financial statements have been retrospectively adjusted for all periods presented to give effect of the reverse stock split.

7. Stock-based Compensation

2017 Stock Incentive Plan

2017 Plan Overview

Prior to August 2015, we did not have our own equity compensation plan. In August 2015, our Board of Directors and our stockholders approved and we adopted the 2015 equity incentive plan, as amended and in effect prior to the closing of our IPO, or the 2015 Plan, which we terminated upon consummation of our IPO and replaced with the 2017 equity incentive plan, or the 2017 Plan. The 2017 Plan provides for the grant of incentive and non-qualified stock options and restricted stock awards to employees, consultants, advisors and directors, as determined by the board of directors. The Company reserved 4,018,538 shares of common stock to be issued under the Plan. The number of shares authorized under the 2017 Plan will be increased each January 1, commencing on January 1, 2018 and ending on (and including) January 1, 2027, by an amount equal to 4% of the outstanding shares of stock outstanding as of the end of the immediately precedeing fiscal year. Notwithstanding the foregoing, our board of directors may act prior to January 1 for a given year to provide that there will be no such January 1 increase in the number of shares authorized under the 2017 Plan for such year, or that the increase in the number of shares authorized under the 2017 Plan for such year will be a lesser number than would otherwise occur pursuant to the preceding sentence. Shares of common stock issued upon exercise of stock options are generally issued from new shares of the Company. The Plan provides that the exercise price of incentive stock options cannot be less than 100% of the fair market value of the common stock on the date of the award for participants who own less than 10% of the total combined voting power of stock of the Company, and not less than 110% for participants who own more than 10% of the Company's voting power. Options and restricted stock granted under the Plan will vest over periods as determined by the Company's board of directors. For options granted to date, the exercise price equaled the fair value of the common stock as determined by the board of directors on the date of grant.

The Company estimates the fair value of stock-based awards to employees and non-employees using the Black-Scholes option-pricing model, which requires the input of highly subjective assumptions, including (a) the expected volatility of the underlying common stock, (b) the expected term of the award, (c) the risk-free interest rate, and (d) expected dividends. Due to the lack of a public market for the trading of its common stock and a lack of company-specific historical and implied volatility data, the Company based its estimate of expected volatility on the historical volatility of a group of companies in the pharmaceutical and biotechnology industries in a similar stage of development as the Company that are publicly traded. For these analyses, the Company selected companies with comparable characteristics to its own including enterprise value, risk profiles and with historical share price information sufficient to meet the expected life of the stock-based awards. The Company computes the historical volatility data using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of its stock-based awards. The Company will continue to apply this process until a sufficient amount of historical information regarding the volatility of its own stock price becomes available. The

(In thousands, except share and per share information)

7. Stock-based Compensation (Continued)

Company estimated the expected life of its employee stock options using the "simplified" method, whereby, the expected life equals the average of the vesting term and the original contractual term of the option. The risk-free interest rates for periods within the expected life of the option are based on the U.S. Treasury yield curve in effect during the period the options were granted.

The Company was historically required to estimate forfeitures at the time of grant, and revise those estimates in subsequent periods if actual forfeitures differ from estimates. The Company used historical data to estimate pre-vesting option forfeitures and record stock-based compensation expense only for those awards that are expected to vest. To the extent that actual forfeitures differ from its estimates, the difference was recorded as a cumulative adjustment in the period the estimates were revised. Stock-based compensation expense recognized in the financial statements is based on awards that are ultimately expected to vest. Upon adopting ASU 2016-09 on January 1, 2017, the Company elected to account for forfeitures as they occur. The adoption did not have a material impact on the Company's financial position, results of operations or cash flows.

The grant date fair value of awards subject to service-based vesting, net of estimated forfeitures, is recognized ratably over the requisite service period, which is generally the vesting period of the respective awards. The Company's stock option awards typically vest over a service period that ranges from three to four years and includes awards with one year cliff vesting followed by ratable monthly and quarterly vesting thereafter and ratable monthly vesting beginning on the grant date.

The unvested portion of stock options granted to non-employees are subject to remeasurement at subsequent reporting periods.

During the years ended December 31, 2017, 2016 and 2015, the Company granted 1,112,717, 164,229 and 900,167 common stock option awards to certain directors, employees and non-employees, respectively.

Using the Black-Scholes option pricing model, the weighted average grant date fair value of options granted to employees and directors during the year ended December 31, 2017 was $4.98.

The fair value of share options granted to employees and directors was estimated at the date of grant using the Black-Scholes option pricing model with the following weighted-average assumptions:

	Year ended December 31,		
	2017	2016	2015
Risk- free interest rate	1.97%	1.39%	1.84%
Expected term (in years)	5.95	6.25	5.93
Expected volatility	66.18%	74.20%	66.50%
Expected dividend yield	—	—	—

Using the Black-Scholes option pricing model, the weighted average grant date fair value of options granted to non-employees during the year ended December 31, 2017 was $5.25.

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

7. Stock-based Compensation (Continued)

The fair value of share options granted to non-employees was estimated at the date of grant using the Black-Scholes option pricing model with the following weighted-average assumptions:

	Year ended December 31,		
	2017	2016	2015
Risk- free interest rate	2.27%	1.58%	2.25%
Expected term (in years)	10.00	10.00	10.00
Expected volatility	74.91%	71.18%	75.70%
Expected dividend yield	—	—	—

A summary of the Company's common stock option activity for the year ended December 31, 2017 is as follows:

	Number of Options	Weighted Average Exercise Price	Weighted-Average Remaining Contractual Term	Aggregate Intrinsic Value
Outstanding as of December 31, 2016	1,064,396	$ 5.32	9.02	$ —
Granted	1,112,717	8.22	—	—
Exercised	(152,671)	4.59	—	588
Cancelled	(191,803)	6.27	—	—
Outstanding as of December 31, 2017	1,832,639	$ 7.04	8.48	$ 40,382
Options vested and expected to vest as of December 31, 2017	1,832,639	$ 7.04	8.48	$ 40,382
Options exercisable at December 31, 2017	535,416	$ 5.53	6.98	$ 12,598

The following summarizes information about stock options at December 31, 2017 by range of exercise prices:

Range of Exercise Prices	Number Oustanding	Weighted Average Remaining Contractual Term	Weighted Average Exercise Price	Number Exercisable	Weighted Average Exercise Price
$4.59 $6.05	650,851	7.26	$ 4.79	309,174	$ 4.59
$6.14 $6.88	930,958	9.34	6.59	143,650	6.41
$7.52 $30.51	250,830	8.44	14.54	82,592	7.52
	1,832,639	8.48	$ 7.04	535,416	$ 5.53

Under the Plan, the Company recorded stock-based compensation of $2,084, $993 and $192 during the year ended December 31, 2017, 2016 and 2015, respectively, that consists of stock-based compensation expense for stock options granted to (or modified for) employees and directors of $1,859, $277 and $39, respectively, and stock options granted to non-employees and employees of the Motus entity that are allocated to the Company of $225, $716 and $153, respectively.

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

7. Stock-based Compensation (Continued)

During 2017, there were three awards subject to modification accounting under ASC 718-20-35-3 through 35-4. Per terms of separation with a former employee, three months of accelerated vesting was granted for the former employee's three stock option awards. As a result, the Company recognized incremental expense for the stock option awards of $254.

As of December 31, 2017, the Company has unrecognized compensation cost of $6,599 related to non-vested employee, non-employee and director awards that is expected to be recognized over a weighted-average period of 2.79 years.

The following table summarizes the classification of the Company's stock-based compensation expenses related to the Plan recognized in the Company's statements of operations and comprehensive loss.

	Year Ended December 31,		
	2017	2016	2015
Research and development	$ 775	$ 343	$ 68
Selling, general, and administrative	1,309	650	124
Total	$ 2,084	$ 993	$ 192

LLC Incentive Plan

The Company was allocated stock compensation expense from the LLC entity's plan using the same proportional use basis for other shared costs (see Note 2). The following table summarizes the classification of the Company's stock-based compensation expenses related to the costs allocated from the LLC's Plan recognized in the Company's statements of operations and comprehensive loss.

	Year Ended December 31,		
	2017	2016	2015
Research and development	$ 152	$ 163	$ 76
General and administrative	42	12	30
Total	$ 194	$ 175	$ 106

The remainder of this Note discloses the stock-based compensation activity of the Predecessor Company and the LLC entity.

Original Plan

The Predecessor Company had one stock based compensation plan—the 2010 equity incentive plan, as amended (the "Original Plan"). The Original Plan previously provided for the grant of incentive and non-qualified stock options and restricted stock grants to employees, consultants, advisors and directors, as determined by the board of directors of the Predecessor Company.

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

7. Stock-based Compensation (Continued)

As a result of the Corporate Reorganization, all outstanding option grants under the Original Plan were cancelled. Each holder of a stock option that was cancelled was issued a restricted common unit of the LLC entity in its place on a one-for-one basis. Restricted common unit vesting agreements were contracted between the LLC entity and the restricted common unit holder granting the holder the same vesting terms as originally granted in the respective option agreement. Any unvested portion of the stock option at the Corporate Reorganization would continue to vest under those original time frames and conditions. Exercise prices were eliminated as they are not applicable to common unit instruments, and all equity incentive grants after the Corporate Reorganization were of restricted common units.

The holder of a restricted common unit is entitled to one vote per unit. After the payment of all preferential amounts to the holders of the convertible preferred units, the holder of a restricted common unit is entitled to his pro rata share of the remaining consideration, if any, based on the number of restricted common units held by the holder.

Restricted Common Units

Upon the Corporate Reorganization, all 615,685 common stock options of the Predecessor Company under the Original Plan outstanding as of March 21, 2013 were exchanged on a one-for-one basis for 615,685 restricted common units of the LLC entity. Vesting continued on the same schedule as originally granted per the respective option agreement. At the time of the exchange, the LLC entity determined the fair value of a restricted common unit to be $1.21 per unit, equivalent to the fair value of a common unit. The fair value of stock options immediately prior to the Corporate Reorganization was determined using a Black-Scholes option pricing model and ranged in value from $0.48 to $0.64. The exchange was accounted for by the LLC entity as a modification in accordance with ASC 718, with the incremental fair value determined to be $255, of which $99 was recognized immediately upon the Corporate Reorganization for the portion related to the vested awards, and the remaining $156 will be recognized over the remaining service period of the restricted common units, net of estimated forfeitures. No common stock options were issued by the Relamorelin Company under the Original Plan subsequent to the Corporate Reorganization.

All restricted common units granted subsequent to the Corporate Reorganization were valued at the fair value of the LLC entity's common unit on the date of grant and will be expensed over their respective service period. Forfeitures are required to be estimated at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from those estimates. The term "forfeitures" is distinct from "cancellations" and represents only the unvested portion of the surrendered unit. Ultimately, the actual expense recognized over the vesting period will only be for those options that vest.

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

7. Stock-based Compensation (Continued)

A summary of the LLC entity's restricted common unit activity for the year ended December 31, 2017 is as follows:

	Number of Units	Weighted-Average Grant Date Fair Value Per Unit
Outstanding unvested as of December 31, 2016	94,617	$ 3.31
Granted	—	—
Vested	(71,048)	2.73
Cancelled	—	—
Outstanding unvested as of December 31, 2017	23,569	$ 5.06

The LLC entity recorded total stock-based compensation expense for restricted common units granted to employees, directors and non-employees of $194, $221 and $337 during the years ended December 31, 2017, 2016 and 2015, respectively. The total fair value of restricted common units vested during the years ended December 31, 2017, 2016 and 2015 was $194, $208 and $309, respectively. As of December 31, 2017, we have unrecognized compensation expense related to the unvested portion of these awards of $119, and we expect to recognize this amount over a weighted-average period of approximately 0.8 years.

2017 Employee Stock Purchase Plan

The Company's board of directors has adopted and the Company's stockholders have approved the 2017 Employee Stock Purchase Plan (the "2017 ESPP"), which became effective in connection with the completion of the Company's IPO in October 2017. A total of 272,841 shares of common stock were reserved for issuance under this plan. In addition, The number of shares authorized under the ESPP will be increased each January 1, commencing on January 1, 2019 and ending on (and including) January 1, 2027, by an amount equal to the lesser of 1% of outstanding shares as of the end of the immediately preceding fiscal year and 682,102. Notwithstanding the foregoing, our board of directors may act prior to January 1 of a given year to provide that there will be no such January 1 increase in the number of shares authorized under the ESPP for such year, or that the increase in the number of shares authorized under the ESPP for such year will be a lesser number than would otherwise occur pursuant to the preceeding sentence. No shares were issued under this plan during the year ended December 31, 2017.

8. Significant Agreements

License Agreements

The Predecessor Company entered into a license agreement on February 26, 2010 with Ipsen Pharma, S.A.S. ("Ipsen") that granted full worldwide right for two programs that include the clinical candidates setmelanotide, which is in Phase 3 clinical trials, and relamorelin, which has completed a Phase 2 clinical trial. As a result of the Corporate Reorganization described in Note 1, the Ipsen license was converted to separate license agreements for the setmelanotide program held by the Company and the relamorelin program held by the Relamorelin Company, respectively. Under the terms of the

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

8. Significant Agreements (Continued)

setmelanotide Ipsen license agreement, assuming that setmelanotide is successfully developed, receives regulatory approval and is commercialized, Ipsen may receive aggregate payments of up to $40,000 upon the achievement of certain development and commercial milestones and royalties on future product sales in the mid-single digits. Substantially all of such aggregate payments of up to $40,000 are for milestones that may be achieved no earlier than first commercial sale of setmelanotide. In the event that the Company executes a sublicense agreement, it shall make payments to Ipsen, depending on the date of such sublicense agreement, ranging from 10% to 20% of all revenues actually received under such sublicense agreement.

In connection with this license agreement, the LLC entity issued two warrants in March 2010 to an affiliate of Ipsen to purchase a total of 489,500 common units. These warrants were vested in full in 2010 and 2011, respectively. In July 2015, the warrant agreement was amended to extend the expiration date to July 31, 2015 as the original warrant agreement expired in March 2015. In July 2015, an affiliate of Ipsen elected to exercise these warrants in full for a total of 489,500 common units of the LLC entity. In July 2015, upon exercise, warrant expense of $923 was allocated to the Company relating to the modification of these warrants and is included within research and development expense.

In January 2016, the Company entered into a licensing agreement with Camurus AB, or Camurus, for the use of Camurus' drug delivery technology. The contract includes a non-refundable and non-creditable signing fee of $500, which was paid during January 2016. The Camurus Agreement also includes up to $7,750 in one-time, non-refundable development milestones achievable upon certain regulatory successes. The Company is also required to pay to Camurus royalties, mid to mid-high single digit, on a product-by-product and country-by-country basis of annual net sales, until the later of (i) 10 years after the date of first commercial sale of such product in such country; or (ii) the expiration of the last to expire valid claim of all licensed patent rights in such country covering such product. The Company is also required to pay one-time, non-refundable, non-creditable sales milestones upon the achievement of certain sales levels for such product and cannot be in excess of $57,000.

In March 2017, the Company achieved the first milestone event associated with this license agreement. The Company completed the first manufactured batch using the Camurus drug delivery technology and filed an investigational new drug application with the FDA. The fee associated with this first milestone was $250 and was recorded as research and development expense.

In December 2017, the Company achieved the second milestone event associated with this license agreement. The Company completed the Phase I proof of concept study using the Camurus drug delivery technology. The fee associated with this second milestone was $1,000 and was recorded as research and development expense.

9. Commitments and Contingencies

The Company is not a party to the lease for the facility it previously shared with the Relamorelin Company. In November 2015, the Company entered into a Lease Agreement for an office facility at 500 Boylston Street, Boston, Massachusetts. The lease term commenced in May 2016 and has a term of 5 years with a five -year renewal option to extend the lease. Rent expense for the years ended December 31, 2017 and 2016 was $215 and $179, respectively.

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

9. Commitments and Contingencies (Continued)

Future minimum payments under the Lease Agreement as of December 31, 2017, are as follows:

2018	$ 298
2019	305
2020	311
2021	131
Total	$ 1,045

10. Related-Party Transactions

The Company shared costs with the Relamorelin Company, its affiliate, including payroll, facilities, information technology and other research and development and general and administrative overhead costs. Additionally, the Relamorelin Company had paid certain Company expenses directly on behalf of the Company. Shared costs incurred by the Relamorelin Company and Company expenses paid by the Relamorelin Company on behalf of the Company are allocated from the Relamorelin Company to the Company as described in Note 1 and Note 2. These net costs totaled $1,570 and $2,149 for the years ended December 31, 2016 and 2015, respectively. The Relamorelin Company was sold to a large pharmaceutical company on December 15, 2016.

The LLC made payments on behalf of the Company totaling $105 related to allocated 2016 employee bonuses. Those costs are recorded as a payable due to the LLC entity from the Company at December 31, 2016 on the balance sheet.

Expenses paid directly by the Company to consultants considered to be related parties amounted to $2,400, $619 and $153 for the years ended December 31, 2017, 2016 and 2015, respectively. Outstanding payments due to these related parties as of December 31, 2017 and 2016 were $90 and $50, respectively and were included within Accounts payable on the balance sheet. Expenses paid by the Relamorelin Company to these related parties amounted to zero, $966 and $1,357 for the years ended December 31, 2017, 2016 and 2015, respectively.

Employees of certain holders of series A and series B convertible preferred units of the LLC entity, have been retained as consultants supporting development activities of the Company and the Relamorelin Company for which the holders are paid cash compensation pursuant to consulting arrangements. Compensation payments related to these consultants totaled $97, $78 and $125 for the years ended December 31, 2017, 2016 and 2015, respectively.

11. Income Tax

In the Company's financial statements, income taxes, including deferred tax balances, have been calculated on a separate tax return basis. Certain of the Company's activities and costs have been included in the tax returns filed by the Relamorelin Company and the LLC entity. Prior to the Corporate Reorganization, the Company's operations were included in the tax returns filed by the Predecessor Company. The Company has filed tax returns on its own behalf since the Corporate Reorganization.

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

11. Income Tax (Continued)

For the years ended December 31, 2017 and 2016, the Company did not have a current or deferred income tax expense or benefit as the entity has incurred losses since inception and has provided a full valuation allowance against its deferred tax assets.

A reconciliation of the income tax benefit at the federal statutory tax rate to the Company's effective income tax rate follows:

	As of December 31,		
	2017	2016	2015
Statutory tax rate	34.00%	34.00%	34.00%
State tax, net of federal benefit	4.08%	2.63%	4.33%
Research and development credit	1.87%	1.34%	0.85%
Orphan drug credit	2.29%	2.15%	1.91%
Non deductible deferred issuance costs	—%	(2.40)%	—%
Tax law change	(27.98)%	—%	—%
Stock compensation	(1.84)%	—%	—%
Investor instrument revaluation	(1.88)%	—%	—%
Non deductible warrant expense	—%	—%	(2.82)%
Other	(0.07)%	(1.32)%	(2.23)%
Change in valuation allowance	(10.47)%	(36.40)%	(36.04)%
Effective tax rate	—%	—%	—%

The principal components of the Company's deferred tax assets are as follows:

	As of December 31,	
	2017	2016
Deferred tax assets:		
Net operating loss carryforwards	$ 18,325	$ 17,248
Research and development credits	2,317	1,214
Orphan drug credit	2,333	1,164
Capitalized license fee	500	600
Other	599	262
Total gross deferred tax assets	24,074	20,488
Valuation allowance	(24,074)	(20,488)
Net deferred tax assets	$ —	$ —

On December 22, 2017, the Tax Cuts and Jobs Act ("The Act"), was signed into law. The Act includes a number of provisions, including the lowering of the U.S. corporate tax rate from 34% to 21%, effective January 1, 2018 and the establishment of a territorial-style system for taxing foreign source income of domestic multinational corporations. The Company is in the process of quantifying the tax impacts of The Act. As a result of The Act, the Company expects there will be one-time adjustments for the re-measurement of deferred tax assets (liabilities). Given the Company's full valuation allowance as of December 31, 2017, the Company does not expect the adjustment to materially impact the Company's

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

11. Income Tax (Continued)

income tax provision or balance sheet. On December 22, 2017, the SEC staff issued Staff Accounting Bulletin No. 118, Income Tax Accounting Implications of the Tax Cuts and Jobs Act, or SAB 118, which allows the recording of provisional amounts during a measurement period not to extend beyond one year of the enactment date. In accordance with SAB 118, we have determined that our deferred tax asset value and associated valuation allowance reduction of $9,432 is a provisional amount and a reasonable estimate at December 31, 2017. The final impact may differ from this provisional amount due to, among other things, changes in interpretations and assumptions we have made thus far and the issuance of additional regulatory or other guidance. We expect to complete the final impact within the measurement period. The Company has quantified the impact of the rate reduction from 34% to 21% in its balance sheet.

ASC 740 requires a valuation allowance to reduce the deferred tax assets reported if, based on the weight of available evidence, it is more likely than not that some portion or all of the deferred tax assets will not be realized. After consideration of all the evidence, both positive and negative, the Company has recorded a full valuation allowance against its deferred tax assets at December 31, 2017 and 2016, because the Company's management has determined that is it more likely than not that these assets will not be realized. The increase in the valuation allowance of $3,586 in 2017 and $9,417 in 2016 primarily relates to the net loss incurred by the Company during each period, partially offset by the federal rate reduction from 34% to 21% as a result of The Act in 2017.

As of December 31, 2017, the Company had federal and state net operating loss carryforwards of approximately $73,109 and $3,763, respectively, which are available to reduce future taxable income. The net operating loss carryforwards expire at various times beginning in 2033 for federal and state purposes.

As of December 31, 2017, the Company had federal and state research tax credits of approximately $1,925 and $496, respectively, which may be used to offset future tax liabilities. Additionally, as of December 31, 2017, the Company had a federal orphan drug credit related to qualifying research of $2,333. These tax credit carryforwards will begin to expire at various times beginning in 2033 for federal purposes and 2028 for state purposes.

The net operating loss and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. Net operating loss and tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant stockholders over a three-year period in excess of 50%, as defined under Sections 382 and 383 of the Internal Revenue Code, respectively, as well as similar state provisions and other provisions within the Internal Revenue Code. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years.

The Company has not recorded any reserves for uncertain tax positions as of December 31, 2017 and 2016. The Company has not, as yet, conducted a study of research and development credit carryforwards. This study may result in an adjustment to the Company's research and development credit carryforwards; however, until a study is completed and any adjustment is known, no amounts are being presented as an uncertain tax position. A full valuation allowance has been provided against the Company's research and development credits and, if an adjustment is required, this adjustment would be offset by an adjustment to

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

11. Income Tax (Continued)

the valuation allowance. Thus, there would be no impact to the balance sheets or statements of operations and comprehensive loss if an adjustment were required.

Interest and penalty charges, if any, related to unrecognized tax benefits will be classified as income tax expense in the accompanying statements of operations and comprehensive loss. As of December 31, 2017 and 2016, the Company had no accrued interest or penalties related to uncertain tax positions.

The Company is subject to examination by the U.S. federal, state and local income tax authorities for tax years 2013 forward. The Company is not currently under examination by the Internal Revenue Service or any other jurisdictions for any tax years.

12. Retrospective Adoption of New Accounting Standard

In November 2016, the FASB issued ASU No. 2016-18, Statement of Cash Flows (Topic 230): Restricted Cash ("ASU 2016-18") that changes the presentation of restricted cash and cash equivalents on the statement of cash flows. ASU 2016-18 requires that restricted cash and restricted cash equivalents be included with cash and cash equivalents when reconciling the beginning-of-period and end-of-period total amounts shown on the statement of cash flows. This amendment is effective for fiscal years beginning after December 15, 2017, including interim periods within those fiscal years, and is applied using retrospective transition method. We adopted ASU on January 1, 2018 and have applied its content to the statement of cash flows for the years ended December 31, 2015, 2016 and 2017 presented herein.

13. Selected Quarterly Financial Data (unaudited)

The following table contains selected quarterly financial information from 2017 and 2016. The Company believes that the following information reflects all normal recurring adjustments necessary for a fair statement of the information for the periods presented. The operating results for any quarter are not necessarily indicative of results for any future period.

	Three months ended			
	March 31, 2017	June 30, 2017	September 30, 2017	December 31, 2017
Total revenue	$ —	$ —	$ —	$ —
Total operating expenses	6,389	6,754	8,286	10,983
Other income (expense), net:	29	(48)	(1,730)	452
Net loss and comprehensive loss	(6,360)	(6,802)	(10,016)	(10,531)
Net loss attributable to common stockholders	$ (7,526)	$ (8,008)	$ (11,429)	$ (10,619)
Net loss attributable to common stockholders per common share, basic and diluted	$ (0.74)	$ (0.78)	$ (1.78)	$ (0.41)

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

13. Selected Quarterly Financial Data (unaudited) (Continued)

	Three months ended			
	March 31, 2016	June 30, 2016	September 30, 2016	December 31, 2016
Total revenue	$ —	$ —	$ —	$ —
Total operating expenses	5,391	5,738	6,401	8,375
Other income (expense), net:	6	8	10	9
Net loss and comprehensive loss	(5,385)	(5,730)	(6,391)	(8,366)
Net loss attributable to common stockholders	$ (6,183)	$ (6,528)	$ (7,191)	$ (9,172)
Net loss attributable to common stockholders per common share, basic and diluted	$ (0.61)	$ (0.64)	$ (0.71)	$ (0.90)

* * * * * *

Rhythm Pharmaceuticals, Inc.

Condensed Consolidated Balance Sheets

(in thousands, except share and per share data)

	(Unaudited) March 31, 2018	December 31, 2017
Assets		
Current assets:		
Cash and cash equivalents	$ 43,167	$ 34,236
Short-term investments	93,286	113,846
Prepaid expenses and other current assets	1,961	2,589
Total current assets	138,414	150,671
Property, plant and equipment, net	779	840
Restricted cash	250	225
Total assets	$ 139,443	$ 151,736
Liabilities, convertible preferred stock and stockholders' equity		
Current liabilities:		
Accounts payable	$ 2,456	$ 2,427
Deferred rent	85	83
Accrued expenses and other current liabilities	3,038	4,210
Total current liabilities	5,579	6,720
Long-term liabilities:		
Deferred rent	206	228
Total liabilities	5,785	6,948
Commitments and contingencies		
Preferred stock:		
Convertible Preferred Stock, $0.001 par value: 10,000,000 shares authorized; no shares issued and outstanding at March 31, 2018 and December 31, 2017, respectively	—	—
Stockholders' equity:		
Common stock, $0.001 par value: 120,000,000 shares authorized; 27,284,140 shares issued and outstanding March 31, 2018 and December 31, 2017, respectively	27	27
Additional paid-in capital	260,342	255,013
Accumulated deficit	(126,711)	(110,252)
Total stockholders' equity	133,658	144,788
Total liabilities, convertible preferred stock and stockholders' equity	$ 139,443	$ 151,736

The accompanying notes are an integral part of these financial statements

Rhythm Pharmaceuticals, Inc.

Condensed Consolidated Statements of Operations and Comprehensive Loss

(in thousands, except share and per share data)

(Unaudited)

	Three months ended March 31,	
	2018	2017
Operating expenses:		
Research and development	$ 12,286	$ 4,873
Selling, general, and administrative	4,715	1,516
Total operating expenses	17,001	6,389
Loss from operations	(17,001)	(6,389)
Other income (expense):		
Interest income, net	542	29
Total other income (expense):	542	29
Net loss and comprehensive loss	$ (16,459)	$ (6,360)
Net loss attributable to common stockholders	$ (16,459)	$ (7,526)
Net loss attributable to common stockholders per common share, basic and diluted	$ (0.60)	$ (0.74)
Weighted average common shares outstanding, basic and diluted	27,284,140	10,196,292

The accompanying notes are an integral part of these financial statements

Rhythm Pharmaceuticals, Inc.

Condensed Consolidated Statements of Cash Flows

(in thousands, except share and per share data)

(Unaudited)

	Three months ended March 31, 2018	Three months ended March 31, 2017
Operating activities		
Net loss	$ (16,459)	$ (6,360)
Adjustments to reconcile net loss to cash used in operating activities:		
Non-cash research and development license expense	4,448	—
Stock-based compensation expense	958	264
Depreciation and amortization	61	54
Non-cash rent expense	(20)	(18)
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	581	(305)
Deferred issuance costs	—	(82)
Accounts payable, accrued expenses and other current liabilities	(1,220)	(464)
Due to related parties	—	(105)
Net cash used in operating activities	(11,651)	(7,016)
Investing activities		
Purchases of short-term investments	(2,023)	(12,009)
Maturities of short-term investments	22,630	3,990
Purchases of property, plant and equipment	—	—
Net cash provided by (used in) investing activities	20,607	(8,019)
Financing activities		
Net proceeds from issuance of Series A Convertible Preferred Stock	—	20,377
Net cash provided by financing activities	—	20,377
Net increase (decrease) in cash, cash equivalents and restricted cash	8,956	5,342
Cash, cash equivalents and restricted cash at beginning of year	34,461	6,765
Cash, cash equivalents and restricted cash at end of year	$ 43,417	$ 12,107

The accompanying notes are an integral part of these financial statements

Rhythm Pharmaceuticals, Inc.

Notes to Unaudited Condensed Consolidated Financial Statements

(In thousands, except share and per share information)

1. Nature of Business

Rhythm Pharmaceuticals, Inc. (the "Company"), is a biopharmaceutical company focused on the development and commercialization of peptide therapeutics for the treatment of genetic deficiencies that result in life-threatening metabolic disorders. The Company's lead product candidate is setmelanotide ("RM-493"), which is a potent, first-in-class, melanocortin-4, or MC4, receptor, agonist for the treatment of rare genetic disorders of obesity caused by MC4 pathway deficiencies. The Company is currently evaluating setmelanotide for the treatment of six genetic disorders of obesity: pro-opiomelanocortin, or POMC, leptin receptor, or LepR, Bardet-Biedl syndrome, Alström syndrome, POMC heterozygous, and POMC epigenetic disorders.

In March 2018 the Company acquired exclusive, worldwide rights from Takeda Pharmaceutical Company Limited ("Takeda") to develop and commercialize T-3525770 (now "RM-853"). RM-853 is a potent, orally available ghrelin o-acyltransferase ("GOAT") inhibitor currently in preclinical development for Prader-Willi Syndrome ("PWS"). PWS is a rare genetic disorder that results in hyperphagia and early-onset, life-threatening obesity, for which there are no approved therapeutic options.

Corporate Reorganization

The Company is a Delaware corporation organized in February 2013 under the name Rhythm Metabolic, Inc. Prior to the Company's organization and the Corporate Reorganization referred to below, the Company was part of Rhythm Pharmaceuticals, Inc. (the "Predecessor Company"), a Delaware corporation which was organized in November 2008 and which commenced active operations in 2010.

In March 2013, the Predecessor Company underwent a corporate reorganization, (the "Corporate Reorganization"), pursuant to which all of the outstanding equity securities of the Predecessor Company were exchanged for units of Rhythm Holding Company, LLC, a newly-organized limited liability company (the "LLC entity"). After the consummation of this exchange and as part of the Corporate Reorganization, the Predecessor Company contributed setmelanotide and the MC4R agonist program to the Company and distributed to the LLC entity all of the then issued and outstanding shares of the Company's stock. The result of the Corporate Reorganization was that the Company and the Predecessor Company became wholly-owned subsidiaries of the LLC entity and the two product candidates and related programs that were originally held by the Predecessor Company were separated, with relamorelin and the ghrelin agonist program being retained by the Predecessor Company and setmelanotide and the MC4R agonist program being held by the Company. The Predecessor Company, after consummation of the Corporate Reorganization, is referred to within these Notes to Financial Statements as the Relamorelin Company and/or Motus.

On October 13, 2015, the Relamorelin Company changed its name to Motus Therapeutics, Inc. ("Motus") and the Company changed its name to Rhythm Pharmaceuticals, Inc. On December 15, 2016, Motus was sold to a large pharmaceutical company. On August 21, 2017, the LLC entity distributed to its members all of its shares of the Company (see Note 5 for further discussion).

Liquidity

The Company has incurred operating losses and negative cash flows from operations since inception. As of March 31, 2018, the Company had an accumulated deficit of $126,711. The Company has primarily funded these losses through capital contributions received from the LLC entity and the sale of preferred

Rhythm Pharmaceuticals, Inc.

Notes to Unaudited Condensed Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

1. Nature of Business (Continued)

and common stock to outside investors. To date, the Company has no product revenue and management expects operating losses to continue for the foreseeable future. The Company has devoted substantially all of its resources to its drug development efforts, comprising research and development, manufacturing, conducting clinical trials for its product candidates, protecting its intellectual property and general and administrative functions relating to these operations. The future success of the Company is dependent on its ability to develop its product candidates and ultimately upon its ability to attain profitable operations. At March 31, 2018, the Company had $136,453 of cash and cash equivalents and short-term investments on hand. In the future, the Company will be dependent on obtaining funding from third parties, such as proceeds from the issuance of debt, sale of equity, and funded research and development programs, to maintain the Company's operations and meet the Company's obligations. There is no guarantee that additional equity or other financings will be available to the Company on acceptable terms, or at all. If the Company fails to obtain additional funding when needed, the Company would be forced to scale back, terminate its operations or seek to merge with or be acquired by another company. Management believes that the Company's existing cash resources will be sufficient to fund the Company's operating plan into the second half of 2019.

2. Summary of Significant Accounting Policies

Basis of Presentation

The Company's unaudited condensed consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States ("GAAP") and the applicable rules and regulations of the Securities and Exchange Commission ("SEC") regarding interim financial reporting. Any reference in these notes to applicable guidance is meant to refer to the authoritative United States generally accepted accounting principles as found in the Accounting Standards Codification ("ASC") and Accounting Standards Updates ("ASU") of the Financial Accounting Standards Board ("FASB"). As permitted under these rules, certain footnotes or other financial information that are normally required by GAAP have been condensed or omitted.

The accompanying interim balance sheet as of March 31, 2018, the statements of operations and comprehensive loss for the three months ended March 31, 2018 and 2017, the statement of cash flows for the three months ended March 31, 2018 and 2017 and the related footnote disclosures are unaudited. In management's opinion, the unaudited interim financial statements have been prepared on the same basis as the audited financial statements and include all adjustments, which include all normal recurring adjustments necessary for the fair presentation of the interim financial statements. The results for the three months ended March 31, 2018 are not necessarily indicative of the results expected for the full fiscal year.

The Company has historically existed and functioned as part of the consolidated businesses of the Predecessor Company. As noted above, the Predecessor Company's setmelanotide and the MC4R agonist program were transferred to the Company as part of the Corporate Reorganization on March 21, 2013. These financial statements include the results of operations of setmelanotide and the MC4R agonist program from its inception.

On September 22, 2017, the Company's board of directors approved a 1-for-9.17 reverse stock split of the Company's issued and outstanding shares of common stock. All share and per share amounts in the

Rhythm Pharmaceuticals, Inc.

Notes to Unaudited Condensed Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

2. Summary of Significant Accounting Policies (Continued)

financial statements have been retrospectively adjusted for all periods presented to give effect of the reverse stock split.

On October 5, 2017, the Company filed an amended and restated certificate of incorporation with the Secretary of State of the State of Delaware to increase its authorized number of shares of common stock to 120,000,000 shares of common stock, $0.001 par value per share and 10,000,000 shares of preferred stock, $0.001 par value per share.

On October 10, 2017 the Company completed its initial public offering ("IPO") of 8,107,500 shares of common stock at an offering price of $17.00 per share, which included the exercise in full by the underwriters of their option to purchase up to 1,057,500 additional shares of common stock. The Company received gross proceeds of approximately $137,828 or net proceeds of $125,658 after deducting underwriting discounts, commissions and estimated offering expenses. In connection with the IPO, the Company's outstanding shares of convertible preferred stock were automatically converted into 17,406,338 shares of common stock.

Use of Estimates

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent liabilities at the date of the financial statements and the reported amounts of revenue and expenses during the reporting period. The Company bases its estimates on historical experience and other market-specific or other relevant assumptions that it believes to be reasonable under the circumstances. This process may result in actual results differing materially from those estimated amounts used in the preparation of the financial statements if these results differ from historical experience, or other assumptions do not turn out to be substantially accurate, even if such assumptions are reasonable when made. Significant estimates relied upon in preparing these financial statements include accrued expenses, stock-based compensation expense, the valuation allowance on the Company's deferred tax assets, and the fair value of the Series A Investor Instrument (see Note 4).

Principles of Consolidation

The consolidated financial statements include the accounts of Rhythm Pharmaceuticals, Inc. and its subsidiaries. All significant intercompany balances and transactions have been eliminated in consolidation.

Off-Balance Sheet Risk and Concentrations of Credit Risk

Financial instruments, which potentially subject the Company to significant concentration of credit risk, consist primarily of cash and cash equivalents and short-term investments, which are maintained at two federally insured financial institutions. The deposits held at these two institutions are in excess of federally insured limits. The Company has not experienced any losses in such accounts and management believes that the Company is not exposed to significant credit risk due to the financial position of the depository institutions in which those deposits are held. The Company has no off-balance sheet risk, such as foreign exchange contracts, option contracts, or other foreign hedging arrangements.

Rhythm Pharmaceuticals, Inc.

Notes to Unaudited Condensed Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

2. Summary of Significant Accounting Policies (Continued)

Segment Information

Operating segments are defined as components of an entity about which separate discrete information is available for evaluation by the chief operating decision maker, or decision-making group, in deciding how to allocate resources and in assessing performance. The Company views its operations and manages its business in one operating segment operating exclusively in the United States.

2017 Series A Investor Instrument

The Company has classified its 2017 Series A Investor Instrument (See Note 4) as a liability as it is a free-standing financial instrument. The 2017 Series A Investor Instrument was recorded at fair value upon the issuance of the Company's series A preferred stock in January 2017, and subsequently remeasured to fair value at each reporting period. Changes in fair value of the financial instrument is recognized as a component of other income (expense), net in the statement of operations and comprehensive loss. The Company estimated the fair value of the 2017 Series A Investor Right/Obligation as the probability-weighted present value of the expected benefit of the investment.

The Company used the Black-Scholes option-pricing model, which incorporates assumptions and estimates, to value the 2017 Series A Investor Call Option and assessed these assumptions and estimates on a quarterly basis as additional information impacting the assumptions was obtained. Estimates and assumptions impacting the fair value measurement include the fair value per share of the underlying series A preferred stock, the expected term of the Series A Investor Call Option, risk-free interest rate, expected dividend yield and expected volatility of the price of the underlying preferred stock. The Company determined the fair value per share of the underlying preferred stock by taking into consideration the most recent sale of our convertible preferred stock and the investors' right to invest in a subsequent tranche. As the Company was a private company and lacked company-specific historical and implied volatility information of its stock, it estimated its expected stock volatility based on the historical volatility of publicly traded peer companies for a term comparable to the estimated term of the Series A Investor Call Option. The risk-free interest rate was determined by reference to the U.S. Treasury yield curve for time periods approximately equal to the estimated term of the Series A Investor Call Option. A dividend yield of zero was assumed. The fair value of the Series A Investor Instrument is determined to be the sum of the fair values of the 2017 Series A Investor Right/Obligation and the 2017 Investor Call Option.

Net Loss Per Share Attributable to Common Shareholders

Basic net loss per share attributable to common stockholders is calculated by dividing net loss attributable to common stockholders by the weighted average shares outstanding during the period, without consideration for Common Stock equivalents. Net loss attributable to common stockholders is calculated by adjusting the net loss of the Company for cumulative preferred stock dividends. During periods of income, the Company allocates participating securities a proportional share of income determined by dividing total weighted average participating securities by the sum of the total weighted average common shares and participating securities (the "two class method"). The Company's convertible preferred stock participates in any dividends declared by the Company and are therefore considered to be participating securities. Participating securities have the effect of diluting both basic and diluted earnings per share during periods of income. During periods of loss, the Company allocates no loss to participating

Rhythm Pharmaceuticals, Inc.

Notes to Unaudited Condensed Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

2. Summary of Significant Accounting Policies (Continued)

securities because they have no contractual obligation to share in the losses of the Company. Diluted net loss per share attributable to common stockholders is calculated by adjusting weighted average shares outstanding for the dilutive effect of Common Stock equivalents outstanding for the period, determined using the treasury-stock and if-converted methods. For purposes of the diluted net loss per share attributable to common stockholders calculation, convertible preferred stock and stock options are considered to be Common Stock equivalents but have been excluded from the calculation of diluted net loss per share attributable to common stockholders, as their effect would be anti-dilutive for all periods presented. Therefore, basic and diluted net loss per share were the same for all periods presented.

The following table includes the potential common shares, presented based on amounts outstanding at each period end, that were excluded from the computation of diluted net loss per share attributable to common stockholders for the periods indicated:

	Three Months Ended March 31,	
	2018	2017
Stock options	2,427,629	1,037,131
Series A convertible preferred shares	—	6,594,870
Total	2,427,629	7,632,001

Basic and diluted earnings per share is calculated as follows:

	Three Months Ended March 31,	
	2018	2017
Numerator:		
Net loss	$ (16,459)	$ (6,360)
Cumulative dividends on convertible preferred shares	—	(1,166)
Loss attributable to common shares—basic and diluted	$ (16,459)	$ (7,526)
Denominator:		
Weighted-average number of common shares—basic and diluted	27,284,140	10,196,292
Loss per common share—basic and diluted	$ (0.60)	$ (0.74)

Subsequent Events

The Company considers events or transactions that occur after the balance sheet date but prior to the issuance of the financial statements to provide additional evidence for certain estimates or to identify matters that require additional disclosure. Subsequent events have been evaluated as required.

Application of New or Revised Accounting Standards

From time to time, new accounting pronouncements are issued by the FASB and adopted by the Company as of the specified effective date. Unless otherwise discussed, the Company believes that the

Rhythm Pharmaceuticals, Inc.

Notes to Unaudited Condensed Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

2. Summary of Significant Accounting Policies (Continued)

impact of recently issued standards that are not yet effective will not have a material impact on its financial position or results of operations upon adoption.

In April 2012, the Jump-Start Our Business Startups Act (the "JOBS Act") was signed into law. The JOBS Act contains provisions that, among other things, reduce certain reporting requirements for an "emerging growth company." As an emerging growth company, the Company elected to not take advantage of the extended transition period afforded by the JOBS Act for the implementation of new or revised accounting standards, and as a result, will comply with new or revised accounting standards on the relevant dates on which adoption of such standards is required for non-emerging growth companies.

In February 2016, the FASB issued ASU 2016-02, Leases (Topic 842). ASU 2016-02 requires lessees to recognize lease assets and lease liabilities for those leases classified as operating leases under previous GAAP. A lessee should recognize in the statement of financial position a liability to make lease payments (the lease liability) and a right-of-use asset representing its right to use the underlying asset for the lease term. For leases with a term of 12 months or less, a lessee is permitted to make an accounting policy election by class of underlying asset not to recognize lease assets and lease liabilities. The recognition, measurement, and presentation of expenses and cash flows arising from a lease by a lessee have not significantly changed from previous GAAP. There continues to be a differentiation between finance leases and operating leases. ASU 2016-02 is effective for fiscal years beginning after December 15, 2018, and interim periods within those fiscal years, and early adoption is permitted. The Company is currently in the process of evaluating the impact of adoption of ASU No. 2016-02 on its financial position and results of operations.

In November 2016, the FASB issued ASU No. 2016-18, Statement of Cash Flows (Topic 230): Restricted Cash ("ASU 2016-18") that changes the presentation of restricted cash and cash equivalents on the statement of cash flows. Restricted cash and restricted cash equivalents will be included with cash and cash equivalents when reconciling the beginning-of-period and end-of-period total amounts shown on the statement of cash flows. This amendment is effective for fiscal years beginning after December 15, 2017, including interim periods within those fiscal years. Early adoption is permitted, including adoption in an interim period. The adoption of this ASU did not have a material impact on the Company's statements of cash flows.

In May 2017, the FASB issued ASU 2017-09, Compensation—Stock Compensation (Topic 718): Scope of Modification Accounting, ("ASU 2017-09"). ASU 2017-09 provides clarity and reduces both (1) diversity in practice and (2) cost and complexity when applying the guidance in Topic 718, to a change to the terms or conditions of a share-based payment award. The amendments in ASU 2017-09 should be applied prospectively to an award modified on or after the adoption date. This ASU is effective for fiscal years, and interim periods within those years, beginning after December 15, 2017. The adoption of this ASU did not have a material impact on the Company's financial position or results of operations.

Rhythm Pharmaceuticals, Inc.

Notes to Unaudited Condensed Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

3. Accrued Expenses

Accrued expenses consisted of the following:

	March 31, 2018	December 31, 2017
Research and development costs	$ 1,426	$ 2,771
Professional fees	1,137	327
Payroll related	462	1,094
Other	13	18
Accrued expenses	$ 3,038	$ 4,210

4. Fair Value of Financial Assets and Liability

As of March 31, 2018 and December 31, 2017, the carrying amount of cash and cash equivalents and short-term investments was $136,453 and $148,082, respectively, which approximates fair value. Cash and cash equivalents and short-term investments includes investments in money market funds that invest in U.S. government securities that are valued using quoted market prices. Accordingly, money market funds and government funds are categorized as Level 1 and had a total balance of $51,742 and $34,698 as of March 31, 2018 and December 31, 2017, respectively. The financial assets valued based on level 2 inputs consist of corporate debt securities and commercial paper, which consist of investments in highly-rated investment-grade corporations.

A financial liability was recognized by the Company during the three months ended March 31, 2017 related to the 2017 Series A Investor Instrument. The liability was valued based on significant inputs not observable in the market, which represents a Level 3 measurement within the fair value hierarchy. Upon the closing of the second tranche of the 2017 Series A preferred financing in August 2017, this liability was settled.

The following tables present information about the Company's financial assets measured at fair value on a recurring basis and indicate the level of the fair value hierarchy utilized to determine such fair values:

	Fair value Measurements as of March 31, 2018 using:			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash Equivalents:				
Corporate Debt Securities and Commercial Paper	$ —	$ 6,989	$ —	$ 6,989
Money Market Funds	36,779	—	—	36,779
Marketable Securities:				
Corporate Debt Securities and Commercial Paper	—	78,323	—	78,323
U.S. Treasury Securities	14,963	—	—	14,963
Total	$ 51,742	$ 85,312	$ —	$ 137,054

Rhythm Pharmaceuticals, Inc.

Notes to Unaudited Condensed Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

4. Fair Value of Financial Assets and Liability (Continued)

	Fair value Measurements as of December 31, 2017 using:			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash Equivalents:				
Corporate Debt Securities	$ —	$ 15,104	$ —	$ 15,104
Money Market Funds	17,753	—	—	17,753
Marketable Securities:				
Corporate Debt Securities	—	96,901	—	96,901
U.S. Treasury Securities	16,945	—	—	16,945
Total	$ 34,698	$ 112,005	$ —	$ 146,703

Marketable Securities

The following tables summarize the Company's marketable securities:

	March 31, 2018			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Assets				
Corporate Debt Securities and Commercial Paper (due within 1 year)	$ 78,528	$ —	$ (205)	$ 78,323
U.S. Treasury Securities (due within 1 year)	14,979	—	(16)	14,963
	$ 93,507	$ —	$ (221)	$ 93,286

	December 31, 2017			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Assets				
Corporate Debt Securities (due within 1 year)	$ 97,029	$ —	$ (128)	$ 96,901
U.S. Treasury Securities (due within 1 year)	16,958	—	(13)	16,945
	$ 113,987	$ —	$ (141)	$ 113,846

Rhythm Pharmaceuticals, Inc.

Notes to Unaudited Condensed Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

4. Fair Value of Financial Assets and Liability (Continued)

Below is a roll forward of the fair value of the 2017 Series A Investor Instrument for the three months ended March 31, 2017:

	2017 Series A Investor Instrument
Fair value at December 31, 2016	$ —
Fair value upon the January 2017 Initial Closing, net	328
Change in fair value	—
Fair value at March 31, 2017	$ 328

The fair value of the Series A Investor Instrument is the sum of the probability-weighted fair value of the 2017 Investor Right/Obligation and the 2017 Series A Call Option.

The following assumptions and inputs were used in determining the fair value of the 2017 Series A Investor Call Option valued using the Black- Scholes option pricing model:

	March 31, 2017
Series A Convertible Preferred Stock Exercise Price	$ 1.00
Series A Convertible Preferred Stock Fair Value	$ 1.39
Expected term	3.5 months
Expected volatility	82.0%
Expected interest rate	0.76%
Expected dividend yield	—

In August 2017, upon the closing of the second tranche of the series A preferred stock financing, the 2017 Series A Investor Call Option expired unexercised.

The Company estimated the fair value of the 2017 Series A Investor Right/Obligation as the probability-weighted present value of the expected benefit of the investment. The expected benefit is the difference between the expected future value of shares issued upon the second tranche closing and the investment price for the second tranche closing. The expected future value is estimated as a weighted average of IPO and remain private scenarios, and the future value is converted to a present value assuming a closing date of October 15, 2017 and a nominal, risk-free discount rate.

5. Preferred and Common Stock

Preferred Stock

Upon the closing of the IPO, the series A convertible preferred stock automatically converted into shares of common stock on a 9.17-for-1 basis.

Common Stock

In March 2013, the Company issued 10,196,292 shares of common stock at a purchase price of $0.001 per share. Prior to August, 2017, the LLC entity owned all of these shares.

Rhythm Pharmaceuticals, Inc.

Notes to Unaudited Condensed Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

5. Preferred and Common Stock (Continued)

On August 21, 2017, the LLC entity exchanged 8,578,646 of its shares of the Company's common stock for 78,666,209 shares of the Company's series A-1 junior preferred stock and the LLC entity distributed all of its shares of the Company's series A-1 junior preferred stock to the holders of its preferred units and the remaining 1,617,646 shares of its common stock to the holders of its common units. Following this distribution, the LLC entity no longer owns any of the Company's shares. The series A-1 junior preferred stock is not redeemable and does not have a stated dividend or liquidation preference. These shares converted to common stock on a 9.17-to-1 basis upon the closing of the IPO in October 2017.

In September 2017, the Company's board of directors approved a 1-for-9.17 reverse stock split of the Company's issued and outstanding shares of common stock. All shares and per share amounts in the financial statements have been retrospectively adjusted for all periods presented to give effect of the reverse stock split.

On October 10, 2017 the Company completed its IPO of 8,107,500 shares of common stock at an offering price of $17.00 per share, which included the exercise in full by the underwriters of their option to purchase up to 1,057,500 additional shares of common stock. The Company received gross proceeds of approximately $137,828 or net proceeds of $125,658 after deducting underwriting discounts, commissions and estimated offering expenses. In connection with the IPO, the Company's outstanding shares of convertible preferred stock were automatically converted into 17,406,338 shares of common stock.

On April 3, 2018, in association with the Takeda license agreement, the Company issued 223,544 shares of common stock. See Note 6 for further discussion.

6. Significant Agreements

License Agreements

The Predecessor Company entered into a license agreement on February 26, 2010 with Ipsen Pharma, S.A.S. ("Ipsen") that granted full worldwide right for two programs that include the clinical candidates setmelanotide, which is in Phase 3 clinical trials, and relamorelin. As a result of the Corporate Reorganization described in Note 1, the Ipsen license was converted to separate license agreements for the setmelanotide program held by the Company and the relamorelin program held by the Relamorelin Company, respectively. Under the terms of the setmelanotide Ipsen license agreement, assuming that setmelanotide is successfully developed, receives regulatory approval and is commercialized, Ipsen may receive aggregate payments of up to $40,000 upon the achievement of certain development and commercial milestones and royalties on future product sales in the mid-single digits. Substantially all of such aggregate payments of up to $40,000 are for milestones that may be achieved no earlier than first commercial sale of setmelanotide. In the event that the Company executes a sublicense agreement, it shall make payments to Ipsen, depending on the date of such sublicense agreement, ranging from 10% to 20% of all revenues actually received under such sublicense agreement.

In July 2017, the Company made a prepayment on the first milestone event associated with this license agreement. The first milestone relates to the initiation of a Phase 3 study for setmelanotide in a pivotal multi-center human clinical trial in a large number of patients. The prepayment associated with this milestone was $1,000 and was recorded as research and development expenses during the three months ended March 31, 2018 when the milestone criteria was met in full.

Rhythm Pharmaceuticals, Inc.

Notes to Unaudited Condensed Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

6. Significant Agreements (Continued)

In January 2016, the Company entered into a license agreement with Camurus AB, or Camurus, for the use of Camurus' drug delivery technology. The contract includes a non-refundable and non-creditable signing fee of $500, which was paid during January 2016. The Camurus agreement also includes up to $7,750 in one-time, non-refundable development milestones achievable upon certain regulatory successes. The Company is also required to pay to Camurus, mid to mid-high single digit royalties, on a product-by-product and country-by-country basis of annual net sales, until the later of (i) 10 years after the date of first commercial sale of such product in such country; or (ii) the expiration of the last to expire valid claim of all licensed patent rights in such country covering such product. The Company is also required to pay one-time, non-refundable, non-creditable sales milestones upon the achievement of certain sales levels for such product that cannot be in excess of $57,000.

In March 2017, the Company achieved the first milestone event associated with this license agreement. The Company completed the first manufactured batch using the Camurus drug delivery technology and filed an investigational new drug application with the FDA. The fee associated with this milestone was $250.

In December 2017, the Company achieved the second milestone event associated with this license agreement. The Company completed the Phase I proof of concept study using the Camurus drug delivery technology. The fee associated with this second milestone was $1,000 and was recorded as research and development expense.

In March 2018, the Company entered into a license agreement with Takeda, for the rights of a program that includes the clinical candidate RM-853, which is a GOAT inhibitor, which is currently in preclinical development for PWS. Pursuant to the license agreement the Company was required to pay a non-refundable and non-creditable signing fee, which the Company settled by issuing on April 3, 2018, 223,544 shares of common stock valued at $4,448. Under the terms of the license agreement, assuming that RM-853 is successfully developed, receives regulatory approval and is commercialized, the Company is also required to pay up to $70,000 in one-time, non-refundable development milestone payments upon the achievement of certain clinical and regulatory milestones. The Company is also required to pay up to $70,000 in one-time, non-refundable, non-creditable sales milestone payments upon the achievement of certain sales levels. The Company is also required to pay to Takeda, mid to mid-high single digit royalties (subject to certain potential reductions over time), on a product-by-product and country-by-country basis of annual net sales, of each product in such country, beginning on the first commercial sale of a product in such country, and continuing until the latest of (i) 10 years after the date of first commercial sale of such product in such country; or (ii) the expiration of the last to expire valid claim of a Takeda patents covering the composition or use of such product in such country; or (iii) the expiration of all regulatory exclusivity for such product in such country. The Company recorded the fair value of the common stock to be issued to the licensors as research and development expense, as the license does not have a future alternative use, in accordance with ASC Topic 730, *Research and Development.* As the shares were not issued prior to the end of the period, the Company evaluated the forward contract and concluded that it met the criteria for equity classification and such amounts have been recorded within additional paid-in capital as of March 31, 2018.

Rhythm Pharmaceuticals, Inc.

Notes to Unaudited Condensed Consolidated Financial Statements (Continued)

(In thousands, except share and per share information)

7. Related-Party Transactions

Expenses paid directly to consultants considered to be related parties amounted to $472 and $229 for the three months ended March 31, 2018 and 2017, respectively. Outstanding payments due to these related parties as of March 31, 2018 and December 31, 2017 were $102 and $112, respectively, and were included within accounts payable on the balance sheet.

8. Income Taxes

For the year ended December 31, 2017, the Company did not have a current or deferred income tax expense or benefit as the entity has incurred losses since inception and has provided a full valuation allowance against its deferred tax assets.

* * * * * *

$150,000,000

Common Stock

PROSPECTUS

MORGAN STANLEY *BofA MERRILL LYNCH* *COWEN*

NEEDHAM & COMPANY

, 2018

PART II
INFORMATION NOT REQUIRED IN PROSPECTUS

Item 13. Other Expenses of Issuance and Distribution.

The following table sets forth the fees and expenses in connection with the issuance and distribution of the securities being registered (excluding the underwriting discount). Except for the SEC registration fee and the FINRA filing fee, all amounts are estimates.

	Amount Paid or to be Paid
SEC registration fee	$ 21,477
FINRA filing fee	26,375
Legal fees and expenses	500,000
Accounting fees and expenses	40,000
Printing expenses	125,000
Transfer and registrar fee	5,000
Miscellaneous	22,148
Total	$ 740,000

Item 14. Indemnification of Directors and Officers.

Section 145 of the Delaware General Corporation Law authorizes a corporation's board of directors to grant, and authorizes a court to award, indemnity to officers, directors, and other corporate agents.

As permitted by Delaware law, our amended and restated certificate of incorporation provides that, to the fullest extent permitted by Delaware law, no director will be personally liable to us or our stockholders for monetary damages for breach of fiduciary duty as a director. Pursuant to Delaware law such protection would be not available for liability:

- for any breach of a duty of loyalty to us or our stockholders;
- for acts or omissions not in good faith or that involve intentional misconduct or a knowing violation of law;
- for any transaction from which the director derived an improper benefit; or
- for an act or omission for which the liability of a director is expressly provided by an applicable statute, including unlawful payments of dividends or unlawful stock repurchases or redemptions as provided in Section 174 of the Delaware General Corporation Law.

Our amended and restated certificate of incorporation also provides that if Delaware law is amended after the approval by our stockholders of the amended and restated certificate of incorporation to authorize corporate action further eliminating or limiting the personal liability of directors, then the liability of our directors will be eliminated or limited to the fullest extent permitted by Delaware law.

Our amended and restated bylaws further provide that we must indemnify our directors and officers to the fullest extent permitted by Delaware law. Our amended and restated bylaws also authorize us to indemnify any of our employees or agents and permit us to secure insurance on behalf of any officer, director, employee or agent for any liability arising out of his or her action in that capacity, whether or not Delaware law would otherwise permit indemnification.

In addition, our amended and restated bylaws also provide that we are required to advance expenses to our directors and officers as incurred in connection with legal proceedings against them for which they may be indemnified and that the rights conferred in the amended and restated bylaws are not exclusive.

We have entered into indemnification agreements with each of our directors and executive officers. These agreements, among other things, require us to indemnify each director and officer to the fullest extent permitted by Delaware law, the amended and restated certificate of incorporation and amended and restated bylaws, for expenses such as, among other things, attorneys' fees, judgments, fines, and settlement amounts incurred by the director or executive officer in any action or proceeding, including any action by or in our right, arising out of the person's services as our director or executive officer or as the director or executive officer of any subsidiary of ours or any other company or enterprise to which the person provides services at our request. We also have directors' and officers' liability insurance.

The SEC has taken the position that personal liability of directors for violation of the federal securities laws cannot be limited and that indemnification by us for any such violation is unenforceable. The limitation of liability and indemnification provisions in our amended and restated certificate of incorporation and amended and restated bylaws may discourage stockholders from bringing a lawsuit against our directors and officers for breach of their fiduciary duty. They may also reduce the likelihood of derivative litigation against our directors and officers, even though an action, if successful, might benefit us and other stockholders. Further, a stockholder's investment may be adversely affected to the extent that we pay the costs of settlement and damage awards against directors and officers as required by these indemnification provisions.

Item 15. Recent Sales of Unregistered Securities

Set forth below is information regarding securities we have issued within the past three years that were not registered under the Securities Act:

On January 6, 2017 and August 18, 2017 we issued 20,475,001 shares and 20,474,998 shares, respectively, of series A preferred stock, $0.001 par value per share, to a number of accredited investors for $1.00 per share. These shares were issued in reliance on Regulation D, Rule 506 and/or Section 4(a)(2) under the Securities Act.

From January 1, 2015 through the consummation of our initial public offering in October 2017, we granted options under the 2015 Plan to purchase an aggregate of 2,150,911 shares of our common stock to employees, consultants and directors, having exercise prices ranging from $4.59 to $26.26 per share. During this period, 152,671 stock options were exercised and 114,503 were forfeited under the 2015 Plan. The 2015 Plan was terminated upon the consummation of our initial public offering. These options and their exercises were granted or issued in reliance on Rule 701 and/or Section 4(a)(2) under the Securities Act.

On April 3, 2018, we issued 223,544 shares of our common stock to Takeda Pharmaceutical Company Limited at a price per share of $17.96. These shares were issued in reliance on Section 4(a)(2) under the Securities Act.

Item 16. Exhibits and Financial Statement Schedules.

(a) Exhibits

The exhibits to the registration statement are listed in the Exhibit Index attached hereto and incorporated by reference herein.

(b) Financial Statement Schedules

All financial statement schedules have been omitted because they are not required or because the required information is given in the financial statements or notes to those statements.

Item 17. Undertakings.

Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers and controlling persons of the Registrant pursuant to the foregoing provisions, or otherwise, the Registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the Registrant of expenses incurred or paid by a director, officer or controlling person of the Registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the Registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Act and will be governed by the final adjudication of such issue.

The undersigned Registrant hereby undertakes that:

(1) For purposes of determining any liability under the Securities Act, the information omitted from the form of prospectus filed as part of this registration statement in reliance upon Rule 430A and contained in a form of prospectus filed by the Registrant pursuant to Rule 424(b)(1) or (4) or 497(h) under the Securities Act shall be deemed to be part of this registration statement as of the time it was declared effective.

(2) For the purpose of determining any liability under the Securities Act, each post-effective amendment that contains a form of prospectus shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof.

EXHIBIT INDEX

Exhibit Number	Exhibit Description	Incorporated by Reference		
		Form	Date	Number
1.1	Form of Underwriting Agreement.			
3.1	Amended and Restated Certificate of Incorporation.	S-1/A	9/25/2017	3.3
3.2	Amended and Restated Bylaws.	S-1/A	9/25/2017	3.5
4.1	Form of Common Stock Certificate.	S-1/A	9/25/2017	4.1
4.2	Amended and Restated Investors' Rights Agreement, dated August 21, 2017.	S-1	9/5/2017	4.2
5.1	Opinion of Morgan, Lewis & Bockius LLP.			
10.1†	Form of Indemnification Agreement.	S-1/A	9/25/2017	10.1
10.2†	2017 Equity Incentive Plan and Form of Option Agreement and Notice of Exercise.	10-Q	11/14/2017	10.2
10.3‡	License Agreement, dated March 21, 2013, by and between the Registrant (f/k/a Rhythm Metabolic, Inc.) and Ipsen Pharma S.A.S.	S-1	9/5/2017	10.6
10.4‡	Development and Manufacturing Services Agreement, dated July 17, 2013, by and between the Registrant (f/k/a Rhythm Metabolic, Inc.) and Peptisyntha Inc. (n/k/a Corden Pharma International).	S-1	9/5/2017	10.7
10.5‡	License Agreement dated January 4, 2016, by and between the Registrant and Camurus AB.	S-1	9/5/2017	10.8
10.6	Amended and Restated Payroll Services Agreement, dated March 21, 2013, by and between the Registrant (f/k/a Rhythm Metabolic, Inc.) and Rhythm Pharmaceuticals, Inc.	S-1	9/5/2017	10.9
10.7†	Rhythm Pharmaceuticals, Inc. 2017 Employee Stock Purchase Plan.	10-Q	11/14/2017	10.10
10.8	Lease, dated November 25, 2015, by and between 500 Boylston & 222 Berkeley Owner (DE) LLC and the Registrant.	S-1	9/5/2017	10.11
10.9†	Consulting Agreement, dated June 12, 2017, by and between the Registrant and Bart Henderson.	S-1	9/5/2017	10.12
10.10†	Offer Letter, dated September 13, 2017, by and between the Registrant and Keith M. Gottesdiener.	S-1/A	9/25/2017	10.13
10.11	Development and Manufacturing Services Agreement, dated as of December 21, 2016, by and between Registrant and Recipharm Monts S.A.S.	S-1	9/5/2017	10.15
10.12†	Offer Letter, dated September 13, 2017, by and between the Registrant and Hunter Smith.	S-1/A	9/25/2017	10.18

Exhibit Number	Exhibit Description	Incorporated by Reference		
		Form	Date	Number
10.13†	Offer Letter, dated September 13, 2017, by and between the Registrant and Nithya Desikan.	S-1/A	9/25/2017	10.19
10.14†	Summary of Non-Employee Director Compensation Policy.	10-Q	5/14/18	10.2
10.15†	2015 Equity Incentive Plan and Form of Option Agreement and Notice of Exercise.	S-1/A	9/25/2017	10.21
10.16‡	License Agreement, dated March 30, 2018, by and between Registrant and Takeda Pharmaceutical Company Limited.	10-Q	5/14/18	10.1
10.17†	First Amendment to the 2017 Employee Stock Purchase Plan.			
21.1	List of Subsidiaries.			
23.1	Consent of Ernst & Young LLP, Independent Registered Public Accounting Firm.			
23.2	Consent of Morgan, Lewis & Bockius LLP (included in Exhibit 5.1).			
24.1	Power of Attorney (included on signature page to this prospectus).			
101.INS	XBRL Instance Document.			
101.SCH	XBRL Taxonomy Extension Schema Document.			
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document.			
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document.			
101.LAB	XBRL Taxonomy Extension Label Linkbase Document.			
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document.			

† Indicates management contract or compensatory plan.
‡ Indicates confidential treatment has been granted with respect to specific portions of this exhibit.

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, as amended, the Registrant has duly caused this Registration Statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Boston, Commonwealth of Massachusetts on June 18, 2018.

RHYTHM PHARMACEUTICALS, INC.

By: /s/ KEITH M. GOTTESDIENER

Keith M. Gottesdiener
Chief Executive Officer, President and Director

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Keith M. Gottesdiener and Hunter C. Smith his true and lawful attorney-in-fact and agent with full power of substitution, for him and in his name, place and stead, in any and all capacities, to sign any and all amendments (including post-effective amendments) to this registration statement, and to sign any registration statement for the same offerings covered by the registration statement that is to be effective upon filing pursuant to Rule 462(b) promulgated under the Securities Act, and all post-effective amendments thereto, and to file the same, with all exhibits thereto and all documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorney-in-fact and agent, full power and authority to do and perform each and every act and thing requisite and necessary to be done in and about the premises, as fully to all intents and purposes as he might or could do in person, hereby ratifying and confirming that all said attorneys-in-fact and agents or any of them, or his or their substitute or substitutes, may lawfully do or cause to be done by virtue hereof

Pursuant to the requirements of the Securities Act, this Registration Statement has been signed by the following persons in the capacities and on the dates indicated.

Name	Title	Date
/s/ KEITH M. GOTTESDIENER Keith M. Gottesdiener	Chief Executive Officer, President and Director (Principal Executive Officer)	June 18, 2018
/s/ HUNTER C. SMITH Hunter C. Smith	Chief Financial Officer and Treasurer (Principal Financial and Accounting Officer)	June 18, 2018
/s/ NEIL EXTER Neil Exter	Director	June 18, 2018
/s/ TODD FOLEY Todd Foley	Director	June 18, 2018

Name	Title	Date
/s/ CHRISTOPHE R. JEAN Christophe R. Jean	Director	June 18, 2018
/s/ ED MATHERS Ed Mathers	Director	June 18, 2018
/s/ DAVID W. J. MCGIRR David W. J. McGirr	Director	June 18, 2018
/s/ DAVID P. MEEKER David P. Meeker	Director, Chairman of the Board	June 18, 2018

Exhibit 1.1

Shares

Rhythm Pharmaceuticals, Inc.

Common Stock
($0.001 par value)

UNDERWRITING AGREEMENT

, 2018

, 2018

Morgan Stanley & Co. LLC
Merrill Lynch, Pierce, Fenner & Smith
Incorporated
Cowen and Company, LLC
c/o Morgan Stanley & Co. LLC
1585 Broadway
New York, New York 10036

Ladies and Gentlemen:

Rhythm Pharmaceuticals, Inc., a Delaware corporation (the "**Company**"), proposes to issue and sell to the several Underwriters named in Schedule I hereto (the "**Underwriters**"), for whom you (the "**Representatives**") are acting as representatives, shares of its common stock, $0.001 par value per share (the "**Firm Shares**"). The Company also proposes to issue and sell to the several Underwriters not more than an additional shares of its common stock, $0.001 par value per share (the "**Additional Shares**") if and to the extent that you, as Managers of the offering, shall have determined to exercise, on behalf of the Underwriters, the right to purchase such shares of common stock granted to the Underwriters in Section 2 hereof. The Firm Shares and the Additional Shares are hereinafter collectively referred to as the "**Shares.**" The shares of common stock, $0.001 par value per share, of the Company to be outstanding after giving effect to the sales contemplated hereby are hereinafter referred to as the "**Common Stock.**"

The Company has filed with the Securities and Exchange Commission (the "**Commission**") a registration statement, including a prospectus, relating to the Shares. The registration statement as amended at the time it becomes effective, including the information (if any) deemed to be part of the registration statement at the time of effectiveness pursuant to Rule 430A under the Securities Act of 1933, as amended (the "**Securities Act**"), is hereinafter referred to as the "**Registration Statement**"; the prospectus in the form first used to confirm sales of Shares (or in the form first made available to the Underwriters by the Company to meet requests of purchasers pursuant to Rule 173 under the Securities Act) is hereinafter referred to as the "**Prospectus.**" If the Company has filed an abbreviated registration statement to register additional shares of Common Stock pursuant to Rule 462(b) under the Securities Act (the "**Rule 462 Registration Statement**"), then any reference herein to the term "**Registration Statement**" shall be deemed to include such Rule 462 Registration Statement.

For purposes of this Agreement, "**free writing prospectus**" has the meaning set forth in Rule 405 under the Securities Act, "**Time of Sale Prospectus**" means the preliminary prospectus together with the documents and pricing information set forth in Schedule II hereto, and "**broadly available road show**" means a "bona fide electronic road show" as defined in Rule 433(h)(5) under the Securities Act that has been made

available without restriction to any person. As used herein, the terms "Registration Statement," "preliminary prospectus," "Time of Sale Prospectus" and "Prospectus" shall include the documents, if any, incorporated by reference therein as of the date hereof.

1. *Representations and Warranties*. The Company represents and warrants to and agrees with each of the Underwriters that:

(a) The Registration Statement has become effective; no stop order suspending the effectiveness of the Registration Statement is in effect, and no proceedings for such purpose are pending before or threatened by the Commission.

(b) (i) The Registration Statement, when it became effective, did not contain and, as amended or supplemented, if applicable, will not contain any untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein not misleading, (ii) the Registration Statement and the Prospectus comply and, as amended or supplemented, if applicable, will comply in all material respects with the Securities Act and the applicable rules and regulations of the Commission thereunder, (iii) the Time of Sale Prospectus does not, and at the time of each sale of the Shares in connection with the offering when the Prospectus is not yet available to prospective purchasers and at the Closing Date (as defined in Section 4), the Time of Sale Prospectus, as then amended or supplemented by the Company, if applicable, will not, contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements therein, in the light of the circumstances under which they were made, not misleading, (iv) each broadly available road show, if any, when considered together with the Time of Sale Prospectus, does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements therein, in the light of the circumstances under which they were made, not misleading and (v) the Prospectus does not contain and, as amended or supplemented, if applicable, will not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements therein, in the light of the circumstances under which they were made, not misleading, except that the representations and warranties set forth in this paragraph do not apply to statements or omissions in the Registration Statement, the Time of Sale Prospectus or the Prospectus based upon information relating to any Underwriter furnished to the Company in writing by such Underwriter through you expressly for use therein.

(c) The Company is not an "ineligible issuer" in connection with the offering pursuant to Rules 164, 405 and 433 under the Securities Act. Any free writing prospectus that the Company is required to file pursuant to Rule 433(d) under the Securities Act has been, or will be, filed with the Commission in accordance with the requirements of the Securities Act and the applicable rules and regulations of the Commission thereunder. Each free writing prospectus that the Company has filed, or is required to file, pursuant to Rule 433(d) under the Securities Act or that was prepared by or on behalf of or used or referred to by the Company complies or will comply in all material respects with the requirements of the Securities Act and the applicable rules and regulations of the Commission thereunder. Except for the free writing prospectuses, if any, identified in Schedule II hereto, and electronic road shows, if any, each furnished to

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you before first use, the Company has not prepared, used or referred to, and will not, without your prior consent, prepare, use or refer to, any free writing prospectus.

(d) From the time of initial confidential submission of the Registration Statement to the Commission (or, if earlier, the first date on which the Company engaged directly or through any person authorized to act on its behalf in any Testing-the-Waters Communication) through the date hereof, the Company has been and is an "emerging growth company," as defined in Section 2(a) of the Securities Act (an "**Emerging Growth Company**"). "**Testing-the-Waters Communication**" means any oral or written communication with potential investors undertaken in reliance on Section 5(d) of the Securities Act.

(e) The Company (i) has not alone engaged in any Testing-the-Waters Communication (other than Testing-the-Waters Communications with the consent of the Representatives with entities that are qualified institutional buyers within the meaning of Rule 144A under the Securities Act or institutions that are accredited investors within the meaning of Rule 501 under the Securities Act) and (ii) has not authorized anyone other than the Representatives to engage in Testing-the-Waters Communications. The Company reconfirms that the Representatives have been authorized to act on its behalf in undertaking Testing-the-Waters Communications. The Company has not distributed any Written Testing-the-Waters Communications other than those listed on Schedule III hereto. "**Written Testing-the-Waters Communication**" means any Testing-the-Waters Communication that is a written communication within the meaning of Rule 405 under the Securities Act.

(f) As of the time of each sale of the Shares in connection with the offering when the Prospectus is not yet available to prospective purchasers, none of (A) the Time of Sale Prospectus, (B) any free writing prospectus, when considered together with the Time of Sale Prospectus, and (C) any individual Written Testing-the-Waters Communication, when considered together with the Time of Sale Prospectus, included, includes or will include an untrue statement of a material fact or omitted, omits or will omit to state a material fact necessary in order to make the statements therein, in the light of the circumstances under which they were made, not misleading.

(g) The Company has been duly incorporated and is validly existing as a corporation in good standing under the laws of the jurisdiction in which it is chartered or organized with full corporate power and authority to own or lease, as the case may be, and to operate its properties and conduct its business as described in the Prospectus, any free writing prospectus and the Time of Sale Prospectus, and is duly qualified to do business as a foreign corporation and is in good standing under the laws of each jurisdiction which requires such qualification, except where the failure to be so qualified or in good standing would not reasonably be expected, individually or in the aggregate, to have a material adverse effect on the condition (financial or otherwise), prospects, earnings, business or properties of the Company taken as a whole, whether or not arising from transactions in the ordinary course of business (a "**Material Adverse Effect**").

(h) The outstanding shares of capital stock of the Company have been duly and validly authorized and issued and are fully paid and nonassessable; the Shares have been duly and validly authorized and, when issued and delivered to and paid for by the Underwriters pursuant to this Agreement, will be fully paid and nonassessable; the holders of shares of capital stock of the Company are not entitled to preemptive or other rights to subscribe for the Shares; and, except as set forth in the Prospectus, any free writing prospectus and the Time of Sale Prospectus, no options, warrants or other rights to purchase, agreements or other obligations to issue, or rights to convert any obligations into or exchange any securities for, shares of capital stock of or ownership interests in the Company are outstanding. The authorized capital stock of the Company conforms as to legal matters to the description thereof contained in each of the Time of Sale Prospectus and the Prospectus.

(i) The Company does not currently own or control, directly or indirectly, any interest in any other corporation, partnership, trust, joint venture, limited liability company, association, or other business entity. The Company is not a participant in any joint venture, partnership or similar arrangement. For the avoidance of doubt, the Company has no subsidiaries.

(j) There is no contract or other document of a character required to be described in the Registration Statement or Time of Sale Prospectus, or to be filed as an exhibit thereto, which is not described or filed as required (and the Preliminary Prospectus contains in all material respects the same description of the foregoing matters contained in the Time of Sale Prospectus); and the statements in the Prospectus and the Time of Sale Prospectus under the headings "Material United States Federal Income and Estate Tax Consequences to Non-U.S. Holders of Our Common Stock," "Risk Factors—Risks Related to Our Intellectual Property Rights," "Risk Factors—Risks Related To Regulatory Approval and Marketing of Setmelanotide and Other Legal Compliance Matters," "Business—Patents and Proprietary Rights", and "Business—Regulatory Matters," insofar as such statements summarize legal matters, agreements, documents or proceedings discussed therein, are accurate and fair summaries of such legal matters, agreements, documents or proceedings.

(k) This Agreement has been duly authorized, executed and delivered by the Company.

(l) There has not occurred any material adverse change, or any development involving a prospective material adverse change, in the condition, financial or otherwise, or in the earnings, business or operations of the Company from that set forth in the Time of Sale Prospectus.

(m) The Company is not and, after giving effect to the offering and sale of the Shares and the application of the proceeds thereof as described in the Prospectus, any free writing prospectus and the Time of Sale Prospectus, will not be an "investment company" as defined in the Investment Company Act of 1940, as amended.

(n) No consent, approval, authorization, filing with or order of any court or governmental agency or body is required in connection with the transactions contemplated herein, except such as have been obtained under the Securities Act and such as may be required under the blue sky laws of any jurisdiction in connection with the purchase and distribution of the Shares by the Underwriters in the manner contemplated herein and in the Prospectus, any free writing prospectus and the Time of Sale Prospectus.

(o) [Reserved]

(p) Neither the issue and sale of the Shares nor the consummation of any other of the transactions herein contemplated nor the fulfillment of the terms hereof will conflict with, result in a breach or violation of, or imposition of any lien, charge or encumbrance upon any property or assets of the Company pursuant to, (i) the charter or by-laws of the Company, (ii) the terms of any indenture, contract, lease, mortgage, deed of trust, note agreement, loan agreement or other agreement, obligation, condition, covenant or instrument to which the Company is a party or bound or to which its property is subject, or (iii) any statute, law, rule, regulation, judgment, order or decree applicable to the Company of any court, regulatory body, administrative agency, governmental body, arbitrator or other authority having jurisdiction over the Company or any of its properties, except in the case of clauses (ii) and (iii) as would not have a Material Adverse Effect.

(q) No holders of securities of the Company have rights to the registration of such securities under the Registration Statement, except such rights which have been duly waived in accordance with their terms and with the General Corporation Law of the State of Delaware.

(r) The consolidated historical financial statements and schedules of the Company included in the Prospectus, the Time of Sale Prospectus and the Registration Statement present fairly in all material respects the financial condition, results of operations and cash flows of the Company as of the dates and for the periods indicated, comply as to form in all material respects with the applicable accounting requirements of the Securities Act and have been prepared in conformity with generally accepted accounting principles applied on a consistent basis throughout the periods involved (except as otherwise noted therein). The selected financial data set forth under the caption “Selected Financial Information” in the Prospectus, the Time of Sale Prospectus and Registration Statement fairly present, on the basis stated in the Prospectus, the Time of Sale Prospectus and the Registration Statement, the information included therein. The pro forma financial statements included in the Prospectus, the Time of Sale Prospectus and the Registration Statement include assumptions that provide a reasonable basis for presenting the significant effects directly attributable to the transactions and events described therein, the related pro forma adjustments give appropriate effect to those assumptions, and the pro forma adjustments reflect the proper application of those adjustments to the historical financial statement amounts in the pro forma financial statements included in the Prospectus, the Time of Sale Prospectus and the Registration Statement. The pro forma financial statements included in the Prospectus, the Time of

Sale Prospectus and the Registration Statement comply as to form in all material respects with the applicable accounting requirements of Regulation S-X under the Securities Act and the pro forma adjustments have been properly applied to the historical amounts in the compilation of those statements.

(s) No action, suit or proceeding by or before any court or governmental agency, authority or body or any arbitrator involving the Company or its property is pending or, to the knowledge of the Company, threatened that could reasonably be expected to have a Material Adverse Effect, except as set forth in or contemplated in the Prospectus, any free writing prospectus and the Time of Sale Prospectus (exclusive of any supplement thereto).

(t) The Company owns or leases all such properties as are necessary to the conduct of its operations as presently conducted in all material respects.

(u) The Company is not in violation or default of (i) its charter or bylaws, (ii) the terms of any indenture, contract, lease, mortgage, deed of trust, note agreement, loan agreement or other agreement, obligation, condition, covenant or instrument to which it is a party or bound or to which its property is subject, or (iii) any statute, law, rule, regulation, judgment, order or decree of any court, regulatory body, administrative agency, governmental body, arbitrator or other authority having jurisdiction over the Company or any of its properties, as applicable, except in the case of clauses (ii) and (iii), for such breach or violation as would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect.

(v) Ernst & Young LLP, who have certified certain financial statements of the Company and delivered their report with respect to the audited financial statements and schedules included in the Prospectus, any free writing prospectus and the Time of Sale Prospectus, are independent public accountants with respect to the Company within the meaning of the Securities Act and the applicable published rules and regulations thereunder.

(w) There are no transfer taxes or other similar fees or charges under Federal law or the laws of any state, or any political subdivision thereof, required to be paid in connection with the execution and delivery of this Agreement or the issuance by the Company or sale by the Company of the Shares.

(x) The Company has filed all tax returns that are required to be filed or has requested extensions thereof (except in any case in which the failure so to file would not have a Material Adverse Effect, except as set forth in or contemplated in the Prospectus, any free writing prospectus and the Time of Sale Prospectus (exclusive of any supplement thereto)) and has paid all taxes required to be paid by it and any other assessment, fine or penalty levied against it, to the extent that any of the foregoing is due and payable, except for any such assessment, fine or penalty that is currently being contested in good faith or as would not have a Material Adverse Effect.

(y) No labor problem or dispute with the employees of the Company exists or, to the knowledge of the Company, is threatened or imminent, and the Company is not aware of any existing or imminent labor disturbance by the employees of any of its principal suppliers, contractors or customers, that could have a Material Adverse Effect.

(z) The Company is insured by insurers of recognized financial responsibility against such losses and risks and in such amounts as the Company reasonably believes are prudent and customary in the businesses in which it is engaged; all policies of insurance and fidelity or surety bonds insuring the Company or its business, assets, employees, officers and directors are in full force and effect; the Company is in compliance with the terms of such policies and instruments in all material respects; and there are no claims by the Company under any such policy or instrument as to which any insurance company is denying liability or defending under a reservation of rights clause; the Company has not been refused any insurance coverage sought or applied for; and the Company has no reason to believe that it will not be able to renew its existing insurance coverage as and when such coverage expires or to obtain similar coverage from similar insurers as may be necessary to continue its business at a cost that would not have a Material Adverse Effect.

(aa) The Company possesses all licenses, certificates, permits and other authorizations issued by all applicable authorities necessary to conduct its business, except in each case, the lack of which would not reasonably be expected, individually or in the aggregate, to have a Material Adverse Effect, and the Company has not received any notice of proceedings relating to the revocation or modification of any such certificate, authorization or permit which, singly or in the aggregate, if the subject of an unfavorable decision, ruling or finding, would have a Material Adverse Effect.

(bb) The Company maintains a system of internal accounting controls sufficient to provide reasonable assurance that (i) transactions are executed in accordance with management's general or specific authorizations; (ii) transactions are recorded as necessary to permit preparation of financial statements in conformity with generally accepted accounting principles and to maintain asset accountability; (iii) access to assets is permitted only in accordance with management's general or specific authorization; and (iv) the recorded accountability for assets is compared with the existing assets at reasonable intervals and appropriate action is taken with respect to any differences. The Company's internal controls over financial reporting are effective and the Company is not aware of any material weakness in its internal controls over financial reporting.

(cc) The Company maintains "disclosure controls and procedures" (as such term is defined in Rule 13a-15(e) under the Securities Exchange Act of 1934, as amended (the "**Exchange Act**")); such disclosure controls and procedures are effective.

(dd) The Company has not taken, directly or indirectly, without giving effect to any activities of the Underwriters, any action designed to or that would constitute or that might reasonably be expected to cause or result in, under the Exchange Act or otherwise, stabilization or manipulation of the price of any security of the Company to facilitate the sale or resale of the Shares.

(ee) Except in each case as would not reasonably be expected, individually or in the aggregate, to have a Material Adverse Effect, the Company (i) is in compliance with any and all applicable foreign, federal, state and local laws and regulations relating to the protection of human health and safety, the environment or hazardous or toxic substances or wastes, pollutants or contaminants ("**Environmental Laws**"), (ii) has received and is in compliance with all permits, licenses or other approvals required of it under applicable Environmental Laws to conduct its business and (iii) has not received notice of any actual or potential liability under any environmental law. The Company has not been named as a "potentially responsible party" under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended.

(ff) None of the following events has occurred or exists: (i) a failure to fulfill the obligations, if any, under the minimum funding standards of Section 302 of the United States Employee Retirement Income Security Act of 1974, as amended ("**ERISA**"), and the regulations and published interpretations thereunder with respect to a Plan that is required to be funded, determined without regard to any waiver of such obligations or extension of any amortization period that would reasonably be expected to have a Material Adverse Effect; (ii) an audit or investigation by the Internal Revenue Service, the U.S. Department of Labor, the Pension Benefit Guaranty Corporation or any other federal or state governmental agency or any foreign regulatory agency with respect to the employment or compensation of employees by the Company that would reasonably be expected to have a Material Adverse Effect; (iii) any breach of any contractual obligation, or any violation of law or applicable qualification standards, with respect to the employment or compensation of employees by the Company that would reasonably be expected to have a Material Adverse Effect. None of the following events has occurred or is reasonably likely to occur: (i) a material increase in the aggregate amount of contributions required to be made to all Plans in the current fiscal year of the Company compared to the amount of such contributions made in the most recently completed fiscal year of the Company; (ii) a material increase in the "accumulated post-retirement benefit obligations" (within the meaning of Statement of Financial Accounting Standards 106) of the Company compared to the amount of such obligations in the most recently completed fiscal year of the Company; (iii) any event or condition giving rise to a liability under Title IV of ERISA that would reasonably be expected to have a Material Adverse Effect; or (iv) the filing of a claim by one or more employees or former employees of the Company related to their employment that would reasonably be expected to have a Material Adverse Effect. For purposes of this paragraph, the term "Plan" means a plan (within the meaning of Section 3(3) of ERISA) subject to Title IV of ERISA with respect to which the Company may have any liability.

(gg) There is and has been no failure on the part of the Company and any of the Company's directors or officers, in their capacities as such, to comply with any provision of the Sarbanes-Oxley Act of 2002 and the rules and regulations promulgated in connection therewith (the "**Sarbanes-Oxley Act**"), including Section 402 relating to loans.

(hh) (i) None of the Company, or any director, officer, or employee thereof, or, to the Company's knowledge, any agent or representative of the Company, has taken or

will take any action in furtherance of an offer, payment, promise to pay, or authorization or approval of the payment, giving or receipt of money, property, gifts or anything else of value, directly or indirectly, to any government official (including any officer or employee of a government or government-owned or controlled entity or of a public international organization, or any person acting in an official capacity for or on behalf of any of the foregoing, or any political party or party official or candidate for political office) in order to influence official action, or to any person in violation of any applicable anti-corruption laws; (ii) the Company has conducted its business in compliance with applicable anti-corruption laws and has instituted and maintained and will continue to maintain policies and procedures reasonably designed to promote and achieve compliance with such laws and with the representations and warranties contained herein; and (iii) the Company will not use, directly or indirectly, the proceeds of the offering in furtherance of an offer, payment, promise to pay, or authorization of the payment or giving of money, or anything else of value, to any person in violation of any applicable anti-corruption laws.

(ii) The operations of the Company are and have been conducted at all times in material compliance with all applicable financial recordkeeping and reporting requirements, including those of the Bank Secrecy Act, as amended by Title III of the Uniting and Strengthening America by Providing

Appropriate Tools Required to Intercept and Obstruct Terrorism Act of 2001 (USA PATRIOT Act), and the applicable anti-money laundering statutes of jurisdictions where the Company conducts business, the rules and regulations thereunder and any related or similar rules, regulations or guidelines, issued, administered or enforced by any governmental agency (collectively, the "**Anti-Money Laundering Laws**"), and no action, suit or proceeding by or before any court or governmental agency, authority or body or any arbitrator involving the Company with respect to the Anti-Money Laundering Laws is pending or, to the best knowledge of the Company, threatened.

(jj) (i) None of the Company, or any director, officer, or employee thereof, or, to the Company's knowledge, any agent, affiliate or representative of the Company, is an individual or entity ("**Person**") that is, or is owned or controlled by one or more Persons that are

(A) the subject of any sanctions administered or enforced by the U.S. Department of Treasury's Office of Foreign Assets Control ("**OFAC**"), the United Nations Security Council ("**UNSC**"), the European Union ("**EU**"), Her Majesty's Treasury ("**HMT**"), or other relevant sanctions authority (collectively, "**Sanctions**"), or

(B) located, organized or resident in a country or territory that is the subject of Sanctions (including, without limitation, Crimea, Cuba, Iran, North Korea, Sudan and Syria).

(ii) The Company will not, directly or indirectly, use the proceeds of the offering, or lend, contribute or otherwise make available such proceeds to any joint venture partner or other Person:

(A) to fund or facilitate any activities or business of or with any Person or in any country or territory that, at the time of such funding or facilitation, is the subject of Sanctions; or

(B) in any other manner that will result in a violation of Sanctions by any Person (including any Person participating in the offering, whether as underwriter, advisor, investor or otherwise).

(iii) For the past 5 years, the Company has not knowingly engaged in, is not now knowingly engaged in, and will not engage in, any dealings or transactions with any Person, or in any country or territory, that at the time of the dealing or transaction is or was the subject of Sanctions.

(kk) The Company owns, possesses, licenses or has other rights to use, on reasonable terms, all patents, patent applications, trade and service marks, trade and service mark registrations, trade names, copyrights, licenses, inventions, trade secrets, technology, know-how and other intellectual property (collectively, the "**Intellectual Property**") necessary for the conduct of the Company's business in all material respects as now conducted or as proposed in the Prospectus to be conducted. Except as set forth in the Prospectus, any free writing prospectus and the Time of Sale Prospectus under the captions "Risk Factors—Risks Related to Our Intellectual Property Rights" and "Business—Patents and Proprietary Rights," (a) there are no rights of third parties to any such Intellectual Property; (b) to the Company's knowledge, there is no material infringement by third parties of any such Intellectual Property; (c) there is no pending or, to the Company's knowledge, threatened action, suit, proceeding or claim by others challenging the Company's rights in or to any such Intellectual Property, and, except as would not reasonably be expected to have a Material Adverse Effect, the Company is unaware of any facts which would form a reasonable basis for any such claim; (d) there is no pending or, to the Company's knowledge, threatened action, suit, proceeding or claim by others challenging the validity or scope of any such Intellectual Property, and, except as would not reasonably be expected to have a Material Adverse Effect, the Company is unaware of any facts which would form a reasonable basis for any such claim; (e) there is no pending or, to the Company's knowledge, threatened action, suit, proceeding or claim by others that the Company infringes or otherwise violates any patent, trademark, copyright, trade secret or other proprietary rights of others, and, except as would not reasonably be expected to have a Material Adverse Effect, the Company is unaware of any other fact which would form a reasonable basis for any such claim; (f) there is no U.S. patent which contains claims that dominate any Intellectual Property described in the Prospectus, any free writing prospectus and the Time of Sale Prospectus as being owned by or licensed to the Company or that interferes with the issued claims of any such Intellectual Property; and (g) there is no prior art that may render any U.S. patent held by the Company invalid, and all prior art of which the Company is aware that may be material to the validity of a U.S. patent or to the patentability of a U.S. patent application has been disclosed to the U.S. Patent and Trademark Office.

(ll) The statements contained in the Prospectus and the Time of Sale Prospectus under the captions "Risk Factors — Risks Related to Our Intellectual Property

Rights" and "Business — Patents and Proprietary Information," insofar as such statements summarize legal matters, agreements, documents, or proceedings discussed therein, are accurate and fair summaries of such legal matters, agreements, documents or proceedings.

(mm) Except as described in the Registration Statement, the Prospectus, any free writing prospectus and the Time of Sale Prospectus, as applicable, the Company (i) is and at all times has been in compliance with all local, state, federal, national, supranational and foreign statutes, rules and regulations applicable to the ownership, testing, development, manufacture, packaging, processing, use, storage, import, export or disposal of any product manufactured or distributed by the Company, including, without limitation, the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 301 et seq.), and the federal Anti-kickback Statute (42 U.S.C. § 1320a-7b(b)), the regulations promulgated pursuant to such laws, and any successor government programs, and comparable state laws, regulations relating to Good Laboratory Practices and Good Clinical Practices (collectively, the "**Applicable Laws**"), except for such non-compliance as would not, individually or in the aggregate, have a Material Adverse Effect; (ii) has not received any notice from any court or arbitrator or governmental or regulatory authority alleging or asserting non-compliance with any Applicable Laws or any licenses, exemptions, certificates, approvals, clearances, authorizations, permits, registrations and supplements or amendments thereto required by any such Applicable Laws ("**Authorizations**"), except for such non- compliance as would not, individually or in the aggregate, have a Material Adverse Effect; (iii) possesses all material Authorizations and such Authorizations are valid and in full force and effect and is not in violation of any term of any such Authorizations, except for such violations as would not, individually or in the aggregate, have a Material Adverse Effect; (iv) has not received written notice of any claim, action, suit, proceeding, hearing, enforcement, investigation, arbitration or other action from any court or arbitrator or governmental or regulatory authority alleging that any product operation or activity is in violation of any Applicable Laws or Authorizations nor, to the Company's knowledge, is any such claim, action, suit, proceeding, hearing, enforcement, investigation, arbitration or other action threatened, except such as would not, individually or in the aggregate, have a Material Adverse Effect;

(v) has not received written notice that any court or arbitrator or governmental or regulatory authority has taken, is taking or intends to take action to materially limit, suspend, materially modify or revoke any Authorizations nor, to the Company's knowledge, is any such limitation, suspension, modification or revocation threatened, except such as would not, individually or in the aggregate, have a Material Adverse Effect; (vi) has filed, obtained, maintained or submitted all material reports, documents, forms, notices, applications, records, claims, submissions and supplements or amendments as required by any Applicable Laws or Authorizations and that all such reports, documents, forms, notices, applications, records, claims, submissions and supplements or amendments were complete and accurate on the date filed in all material respects (or were corrected or supplemented by a subsequent submission); and (vii) is not a party to any corporate integrity agreements, monitoring agreements, consent decrees, settlement orders, or similar agreements with or imposed by any governmental or regulatory authority.

(nn) Subsequent to the respective dates as of which information is given in each of the Registration Statement, the Time of Sale Prospectus and the Prospectus, (i) the Company has not incurred any material liability or obligation, direct or contingent, nor entered into any material transaction; (ii) the Company has not purchased any of its outstanding capital stock, nor declared, paid or otherwise made any dividend or distribution of any kind on its capital stock other than ordinary and customary dividends; and (iii) there has not been any material change in the capital stock, short-term debt or long-term debt of the Company, except in each case as described in each of the Registration Statement, the Time of Sale Prospectus and the Prospectus, respectively.

(oo) Except as described in the Time of Sale Prospectus, the Company has not sold, issued or distributed any shares of Common Stock during the six-month period preceding the date hereof, including any sales pursuant to Rule 144A under, or Regulation D or S of, the Securities Act, other than shares issued pursuant to employee benefit plans, qualified stock option plans or other employee compensation plans or pursuant to outstanding options, rights or warrants.

(pp) Any certificate signed by any officer of the Company and delivered to the Representatives or counsel for the Underwriters in connection with the offering of the Shares shall be deemed a representation and warranty by the Company, as to matters covered thereby, to each Underwriter.

2. *Agreements to Sell and Purchase.* The Company hereby agrees to sell to the several Underwriters, and each Underwriter, upon the basis of the representations and warranties herein contained, but subject to the conditions hereinafter stated, agrees, severally and not jointly, to purchase from the Company the respective numbers of Firm Shares set forth in Schedule I hereto opposite its name at $[ ] a share (the "**Purchase Price**").

On the basis of the representations and warranties contained in this Agreement, and subject to its terms and conditions, the Company agrees to sell to the Underwriters the Additional Shares, and the Underwriters shall have the right to purchase, severally and not jointly, up to [ ] Additional Shares at the Purchase Price, provided, however, that the amount paid by the Underwriters for any Additional Shares shall be reduced by an amount per share equal to any dividends declared by the Company and payable on the Firm Shares but not payable on such Additional Shares. You may exercise this right on behalf of the Underwriters in whole or from time to time in part by giving written notice not later than 30 days after the date of this Agreement. Any exercise notice shall specify the number of Additional Shares to be purchased by the Underwriters and the date on which such shares are to be purchased. Each purchase date must be at least one business day after the written notice is given and may not be earlier than the closing date for the Firm Shares nor later than ten business days after the date of such notice. Additional Shares may be purchased as provided in Section 4 hereof solely for the purpose of covering sales of shares in excess of the number of the Firm Shares. On each day, if any, that Additional Shares are to be purchased (an "**Option Closing Date**"), each Underwriter agrees, severally and not jointly, to purchase the number of Additional Shares (subject to such adjustments to eliminate fractional shares as you may

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determine) that bears the same proportion to the total number of Additional Shares to be purchased on such Option Closing Date as the number of Firm Shares set forth in Schedule I hereto opposite the name of such Underwriter bears to the total number of Firm Shares.

3. *Terms of Public Offering.* The Company is advised by you that the Underwriters propose to make a public offering of their respective portions of the Shares as soon after the Registration Statement and this Agreement have become effective as in your judgment is advisable. The Company is further advised by you that the Shares are to be offered to the public initially at $[ ] a share (the "**Public Offering Price**") and to certain dealers selected by you at a price that represents a concession not in excess of $[ ] a share under the Public Offering Price, and that any Underwriter may allow, and such dealers may reallow, a concession, not in excess of $[ ] a share, to any Underwriter or to certain other dealers.

4. *Payment and Delivery.* Payment for the Firm Shares shall be made to the Company in Federal or other funds immediately available in New York City against delivery of such Firm Shares for the respective accounts of the several Underwriters at 10:00 a.m., New York City time, on [, 2018], or at such other time on the same or such other date, not later than [, 2018], as shall be designated in writing by you. The time and date of such payment are hereinafter referred to as the "**Closing Date**."

Payment for any Additional Shares shall be made to the Company in Federal or other funds immediately available in New York City against delivery of such Additional Shares for the respective accounts of the several Underwriters at 10:00 a.m., New York City time, on the date specified in the corresponding notice described in Section 2 or at such other time on the same or on such other date, in any event not later than [, 2018], as shall be designated in writing by you.

The Firm Shares and Additional Shares shall be registered in such names and in such denominations as you shall request in writing not later than one full business day prior to the Closing Date or the applicable Option Closing Date, as the case may be. The Firm Shares and Additional Shares shall be delivered to you on the Closing Date or an Option Closing Date, as the case may be, for the respective accounts of the several Underwriters, with any transfer taxes payable in connection with the transfer of the Shares to the Underwriters duly paid, against payment of the Purchase Price therefor.

5. *Conditions to the Underwriters' Obligations.* The obligations of the several Underwriters hereunder are subject to the accuracy of the representations and warranties of the Company contained herein or in certificates of any officer of the Company delivered pursuant to the provisions hereof, to the performance by the Company of its covenants and other obligations hereunder, and to the following further conditions:

(a) Subsequent to the execution and delivery of this Agreement and prior to the Closing Date:

(i) there shall not have occurred any downgrading, nor shall any notice have been given of any intended or potential downgrading or of any review for a possible change that does not indicate the direction of the possible change, in the rating accorded any of the securities of the Company by any "nationally recognized statistical rating organization," as such term is defined in Section 3(a)(62) of the Exchange Act; and

(ii) there shall not have occurred any change, or any development involving a prospective change, in the condition, financial or otherwise, or in the earnings, business or operations of the Company, taken as a whole, from that set forth in the Time of Sale Prospectus that, in your judgment, is material and adverse and that makes it, in your judgment, impracticable to market the Shares on the terms and in the manner contemplated in the Time of Sale Prospectus.

(b) The Underwriters shall have received on the Closing Date a certificate, dated the Closing Date and signed by an executive officer of the Company, to the effect set forth in Section 5(a)(i) above and to the effect that the representations and warranties of the Company contained in this Agreement are true and correct as of the Closing Date and that the Company has complied with all of the agreements and satisfied all of the conditions on its part to be performed or satisfied hereunder on or before the Closing Date.

The officer signing and delivering such certificate may rely upon the best of his or her knowledge as to proceedings threatened.

(c) The Underwriters shall have received on the Closing Date an opinion of Morgan, Lewis & Bockius LLP, outside counsel for the Company, substantially in the form attached hereto as Exhibit A-1.

(d) The Underwriters shall have received on the Closing Date opinions of Hogan Lovells LLP and Hogan Lovells International LLP, special regulatory counsel for the Company, each substantially in the form attached hereto as Exhibit A-2.

(e) The Underwriters shall have received on the Closing Date an opinion of Kendall Square IP Strategies, LLC, special intellectual property counsel for the Company, substantially in the form attached hereto as Exhibit A-3.

(f) The Underwriters shall have received on the Closing Date an opinion of Lando & Anastasi, LLP, special intellectual property counsel for the Company, substantially in the form attached hereto as Exhibit A-4.

(g) The Underwriters shall have received on the Closing Date an opinion of Ropes & Gray LLP, counsel for the Underwriters, dated the Closing Date, with respect to the issuance and sale of the Shares, the Registration Statement, the Prospectus and any free writing prospectus, the Time of Sale Prospectus (together with any supplement thereto) and other related matters as the Representatives may reasonably require, and the

Company shall have furnished to such counsel such documents as they request for the purpose of enabling them to pass upon such matters.

The opinion of Morgan, Lewis & Bockius LLP described in Section 5(c) above shall be rendered to the Underwriters at the request of the Company and shall so state therein.

(h) The Underwriters shall have received, on each of the date hereof and the Closing Date, a letter dated the date hereof or the Closing Date, as the case may be, in form and substance satisfactory to the Underwriters, from Ernst & Young LLP, independent public accountants, containing statements and information of the type ordinarily included in accountants' "comfort letters" to underwriters with respect to the financial statements and certain financial information contained in the Registration Statement, the Time of Sale Prospectus and the Prospectus; *provided* that the letter delivered on the Closing Date shall use a "cut-off date" not earlier than the date hereof.

(i) The "lock-up" agreements, each substantially in the form of Exhibit B hereto, between you and each officer, director and specified stockholders of the Company as set forth in Schedule IV relating to sales and certain other dispositions of shares of Common Stock or certain other securities, delivered to you on or before the date hereof, shall be in full force and effect on the Closing Date.

(j) [Reserved]

(k) The Company will deliver to each Underwriter (or its agent), on the date of execution of this Agreement, a properly completed and executed Certification Regarding Beneficial Owners of Legal Entity Customers (the "Certification"), together with copies of identifying documentation, and the Company undertakes to provide such additional supporting documentation as each Underwriter may reasonably request in connection with the verification of the Certification.

(l) The several obligations of the Underwriters to purchase Additional Shares hereunder are subject to the delivery to you on the applicable Option Closing Date of the following:

(i) a certificate, dated the Option Closing Date and signed by an executive officer of the Company, confirming that the certificate delivered on the Closing Date pursuant to Section 5(b) hereof remains true and correct as of such Option Closing Date;

(ii) an opinion of Morgan, Lewis & Bockius LLP, outside counsel for the Company, dated the Option Closing Date, relating to the Additional Shares to be purchased on such Option Closing Date and otherwise to the same effect as the opinion required by Section 5(c) hereof;

(iii) opinions of Hogan Lovells LLP and Hogan Lovells International LLP, special regulatory counsel for the Company, dated the Option Closing Date, relating to the Additional Shares to be purchased on such Option

Closing Date and otherwise to the same effect as the opinion required by Section 5(d) hereof;

(iv) an opinion of Kendall Square IP Strategies, LLC, special intellectual property counsel for the Company, dated the Option Closing Date, relating to the Additional Shares to be purchased on such Option Closing Date and otherwise to the same effect as the opinion required by Section 5(e) hereof;

(v) an opinion of Lando & Anastasi, LLP, special intellectual property counsel for the Company, dated the Option Closing Date, relating to the Additional Shares to be purchased on such Option Closing Date and otherwise to the same effect as the opinion required by Section 5(f) hereof;

(vi) an opinion of Ropes & Gray LLP, counsel for the Underwriters, dated the Option Closing Date, relating to the Additional Shares to be purchased on such Option Closing Date and otherwise to the same effect as the opinion required by Section 5(g) hereof;

(vii) a letter dated the Option Closing Date, in form and substance satisfactory to the Underwriters, from Ernst & Young LLP, independent public accountants, substantially in the same form and substance as the letter furnished to the Underwriters pursuant to Section 5(h) hereof; *provided* that the letter delivered on the Option Closing Date shall use a "cut-off date" not earlier than three business days prior to such Option Closing Date; and

(viii) such other documents as you may reasonably request with respect to the good standing of the Company, the due authorization and issuance of the Additional Shares to be sold on such Option Closing Date and other matters related to the issuance of such Additional Shares.

6. *Covenants of the Company*. The Company covenants with each Underwriter as follows:

(a) To furnish to you, without charge, three signed copies of the Registration Statement (including exhibits thereto) and for delivery to each other Underwriter a conformed copy of the Registration Statement (without exhibits thereto) and to furnish to you in New York City, without charge, prior to 10:00 a.m. New York City time on the business day next succeeding the date of this Agreement and during the period mentioned in Section 6(e) or 6(f) below, as many copies of the Time of Sale Prospectus, the Prospectus and any supplements and amendments thereto or to the Registration Statement as you may reasonably request.

(b) Before amending or supplementing the Registration Statement, the Time of Sale Prospectus or the Prospectus, to furnish to you a copy of each such proposed amendment or supplement and not to file any such proposed amendment or supplement

to which you reasonably object, and to file with the Commission within the applicable period specified in Rule 424(b) under the Securities Act any prospectus required to be filed pursuant to such Rule.

(c) To furnish to you a copy of each proposed free writing prospectus to be prepared by or on behalf of, used by, or referred to by the Company and not to use or refer to any proposed free writing prospectus to which you reasonably object.

(d) Not to take any action that would result in an Underwriter or the Company being required to file with the Commission pursuant to Rule 433(d) under the Securities Act a free writing prospectus prepared by or on behalf of the Underwriter that the Underwriter otherwise would not have been required to file thereunder.

(e) If the Time of Sale Prospectus is being used to solicit offers to buy the Shares at a time when the Prospectus is not yet available to prospective purchasers and any event shall occur or condition exist as a result of which it is necessary to amend or supplement the Time of Sale Prospectus in order to make the statements therein, in the light of the circumstances, not misleading, or if any event shall occur or condition exist as a result of which the Time of Sale Prospectus conflicts with the information contained in the Registration Statement then on file, or if, in the opinion of counsel for the Underwriters, it is necessary to amend or supplement the Time of Sale Prospectus to comply with applicable law, forthwith to prepare, file with the Commission and furnish, at its own expense, to the Underwriters and to any dealer upon request, either amendments or supplements to the Time of Sale Prospectus so that the statements in the Time of Sale Prospectus as so amended or supplemented will not, in the light of the circumstances when the Time of Sale Prospectus is delivered to a prospective purchaser, be misleading or so that the Time of Sale Prospectus, as amended or supplemented, will no longer conflict with the Registration Statement, or so that the Time of Sale Prospectus, as amended or supplemented, will comply with applicable law.

(f) If, during such period after the first date of the public offering of the Shares as in the opinion of counsel for the Underwriters the Prospectus (or in lieu thereof the notice referred to in Rule 173(a) of the Securities Act) is required by law to be delivered in connection with sales by an Underwriter or dealer, any event shall occur or condition exist as a result of which it is necessary to amend or supplement the Prospectus in order to make the statements therein, in the light of the circumstances when the Prospectus (or in lieu thereof the notice referred to in Rule 173(a) of the Securities Act) is delivered to a purchaser, not misleading, or if, in the opinion of counsel for the Underwriters, it is necessary to amend or supplement the Prospectus to comply with applicable law, forthwith to prepare, file with the Commission and furnish, at its own expense, to the Underwriters and to the dealers (whose names and addresses you will furnish to the Company) to which Shares may have been sold by you on behalf of the Underwriters and to any other dealers upon request, either amendments or supplements to the Prospectus so that the statements in the Prospectus as so amended or supplemented will not, in the light of the circumstances when the Prospectus (or in lieu thereof the notice referred to in Rule 173(a) of the Securities Act) is delivered to a purchaser, be misleading or so that the Prospectus, as amended or supplemented, will comply with applicable law.

(g) To endeavor to qualify the Shares for offer and sale under the securities or Blue Sky laws of such jurisdictions as you shall reasonably request; provided, that in no event shall the Company be obligated to qualify to do business in any jurisdiction where it is not now so qualified or to take any action that would subject it to service of process in suits, other than those arising out of the offering or sale of the Shares, in any jurisdiction where it is now so subject.

(h) To make generally available to the Company's security holders and to you as soon as practicable an earnings statement covering a period of at least twelve months beginning with the first fiscal quarter of the Company occurring after the date of this Agreement which shall satisfy the provisions of Section 11(a) of the Securities Act and the rules and regulations of the Commission thereunder.

(i) Whether or not the transactions contemplated in this Agreement are consummated or this Agreement is terminated, to pay or cause to be paid all expenses incident to the performance of its obligations under this Agreement, including: (i) the fees, disbursements and expenses of the Company's counsel and the Company's accountants in connection with the registration and delivery of the Shares under the Securities Act and all other fees or expenses in connection with the preparation and filing of the Registration Statement, any preliminary prospectus, the Time of Sale Prospectus, the Prospectus, any free writing prospectus prepared by or on behalf of, used by, or referred to by the Company and amendments and supplements to any of the foregoing, including all printing costs associated therewith, and the mailing and delivering of copies thereof to the Underwriters and dealers, in the quantities hereinabove specified, (ii) all costs and expenses related to the transfer and delivery of the Shares to the Underwriters, including any transfer or other taxes payable thereon, (iii) the cost of printing or producing any Blue Sky or Legal Investment memorandum in connection with the offer and sale of the Shares under state securities laws and all expenses in connection with the qualification of the Shares for offer and sale under state securities laws as provided in Section 6(g) hereof, including filing fees and the reasonable fees and disbursements of counsel for the Underwriters (with such fees and disbursements not to exceed $5,000) in connection with such qualification and in connection with the Blue Sky or Legal Investment memorandum, (iv) all filing fees and the reasonable fees and disbursements of counsel to the Underwriters (with such fees and disbursements not to exceed $40,000) incurred in connection with the review and qualification of the offering of the Shares by the Financial Industry Regulatory Authority, (v) all costs and expenses incident to listing the Shares on the NASDAQ Global Market, (vi) the cost of printing certificates representing the Shares, (vii) the costs and charges of any transfer agent, registrar or depositary, (viii) the costs and expenses of the Company relating to investor presentations on any "road show" undertaken in connection with the marketing of the offering of the Shares, including, without limitation, expenses associated with the preparation or dissemination of any electronic road show, expenses associated with the production of road show slides and graphics, fees and expenses of any consultants engaged in connection with the road show presentations with the prior approval of the Company,

travel and lodging expenses of the representatives and officers of the Company and any such consultants, and 50% of the cost of any aircraft chartered in connection with the road show, provided that no aircraft shall be chartered without the prior consent of the Company, and provided further that, for the avoidance of doubt, the Underwriters shall pay their own travel expenses (including lodging, transportation, meals and entertainment), (ix) the document production charges and expenses associated with printing this Agreement and (x) all other costs and expenses incident to the performance of the obligations of the Company hereunder for which provision is not otherwise made in this Section. It is understood, however, that except as provided in this Section, Section 8 entitled "Indemnity and Contribution" and the last paragraph of Section 10 below, the Underwriters will pay all of their costs and expenses, including fees and disbursements of their counsel, stock transfer taxes payable on resale of any of the Shares by them and any advertising expenses connected with any offers they may make.

(j) The Company will promptly notify the Representatives if the Company ceases to be an Emerging Growth Company at any time prior to the later of (a) completion of the distribution of the Shares within the meaning of the Securities Act and (b) completion of the Restricted Period (as defined in this Section 6).

(k) If at any time following the distribution of any Written Testing-the-Waters Communication there occurred or occurs an event or development as a result of which such Written Testing-the-Waters Communication included or would include an untrue statement of a material fact or omitted or would omit to state a material fact necessary in order to make the statements therein, in the light of the circumstances existing at that subsequent time, not misleading, the Company will promptly notify the Representatives and will promptly amend or supplement, at its own expense, such Written Testing-the-Waters Communication to eliminate or correct such untrue statement or omission.

The Company also covenants with each Underwriter that, without the prior written consent of the Representatives on behalf of the Underwriters, it will not, during the period ending 90 days after the date of the Prospectus (the "**Restricted Period**"), (1) offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend, or otherwise transfer or dispose of, directly or indirectly, any shares of Common Stock or any securities convertible into or exercisable or exchangeable for Common Stock or (2) enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of the Common Stock, whether any such transaction described in clause (1) or (2) above is to be settled by delivery of Common Stock or such other securities, in cash or otherwise or (3) except as otherwise permitted herein, file any registration statement with the Commission relating to the offering of any shares of Common Stock or any securities convertible into or exercisable or exchangeable for Common Stock.

The restrictions contained in the preceding paragraph shall not apply to (1) the Shares to be sold hereunder, (2) the issuance by the Company of shares of Common Stock, or any securities convertible into, or exercisable for, shares of Common Stock, pursuant to any employee stock option plan, incentive plan, employee stock purchase

plan or stock ownership plan of the Company in effect on the date hereof and disclosed in the Prospectus, provided that the underlying equity securities shall continue to be subject to the restrictions on transfer set forth in the preceding paragraph during the Restricted Period, (3) the issuance by the Company of shares of Common Stock issuable upon the conversion of securities outstanding on the date hereof, (4) the filing of one or more registration statements on Form S-8, or (5) the offer, issuance and sale of shares of Common Stock or any securities convertible into, or exercisable, or exchangeable for, shares of Common Stock in connection with any acquisition or strategic investment (including any joint venture, strategic alliance or partnership) so long as (x) the aggregate number of shares of Common Stock issued or issuable does not exceed 5% of the number of shares of Common Stock outstanding immediately after the issuance and sale of the securities, and (y) each recipient of any such shares or other securities agrees to restrictions on the resale of securities that are consistent with the lock-up letters described in Section 5(h) hereof for the remainder of the Restricted Period.

7. *Covenants of the Underwriters*. Each Underwriter severally covenants with the Company not to take any action that would result in the Company being required to file with the Commission under Rule 433(d) under the Securities Act a free writing prospectus prepared by or on behalf of such Underwriter that otherwise would not be required to be filed by the Company thereunder, but for the action of the Underwriter.

8. *Indemnity and Contribution.* (a) The Company agrees to indemnify and hold harmless each Underwriter, each person, if any, who controls any Underwriter within the meaning of either Section 15 of the Securities Act or Section 20 of the Exchange Act and each affiliate of any Underwriter within the meaning of Rule 405 under the Securities Act from and against any and all losses, claims, damages and liabilities (including, without limitation, any legal or other expenses reasonably incurred in connection with defending or investigating any such action or claim) caused by any untrue statement or alleged untrue statement of a material fact contained in the Registration Statement or any amendment thereof, any preliminary prospectus, the Time of Sale Prospectus or any amendment or supplement thereto, any issuer free writing prospectus as defined in Rule 433(h) under the Securities Act, any Company information that the Company has filed, or is required to file, pursuant to Rule 433(d) under the Securities Act, any road show as defined in Rule 433(h) under the Securities Act (a "road show"), or the Prospectus or any amendment or supplement thereto, or any Written Testing-the-Waters Communication caused by any omission or alleged omission to state therein a material fact required to be stated therein or necessary to make the statements therein, in the light of the circumstances under which they were made, not misleading, except insofar as such losses, claims, damages or liabilities are caused by any such untrue statement or omission or alleged untrue statement or omission based upon information relating to any Underwriter furnished to the Company in writing by such Underwriter through you expressly for use therein. The Company agrees and confirms that references to "affiliates" of Morgan Stanley that appear in this Agreement shall be understood to include Mitsubishi UFJ Morgan Stanley Securities Co., Ltd.

(b) Each Underwriter agrees, severally and not jointly, to indemnify and hold harmless the Company, its directors, its officers who sign the Registration Statement and

each person, if any, who controls the Company within the meaning of either Section 15 of the Securities Act or Section 20 of the Exchange Act to the same extent as the foregoing indemnity from the Company to such Underwriter, but only with reference to information relating to such Underwriter furnished to the Company in writing by such Underwriter through you expressly for use in the Registration Statement, any preliminary prospectus, the Time of Sale Prospectus, any issuer free writing prospectus, road show or the Prospectus or any amendment or supplement thereto.

(c) In case any proceeding (including any governmental investigation) shall be instituted involving any person in respect of which indemnity may be sought pursuant to Section 8(a) or 8(b), such person (the "**indemnified party**") shall promptly notify the person against whom such indemnity may be sought (the "**indemnifying party**") in writing and the indemnifying party, upon request of the indemnified party, shall retain counsel reasonably satisfactory to the indemnified party to represent the indemnified party and any others the indemnifying party may designate in such proceeding and shall pay the fees and disbursements of such counsel related to such proceeding. In any such proceeding, any indemnified party shall have the right to retain its own counsel, but the fees and expenses of such counsel shall be at the expense of such indemnified party unless (i) the indemnifying party and the indemnified party shall have mutually agreed to the retention of such counsel or (ii) the named parties to any such proceeding (including any impleaded parties) include both the indemnifying party and the indemnified party and representation of both parties by the same counsel would be inappropriate due to actual or potential differing interests between them. It is understood that the indemnifying party shall not, in respect of the legal expenses of any indemnified party in connection with any proceeding or related proceedings in the same jurisdiction, be liable for the fees and expenses of more than one separate firm (in addition to any local counsel) for all such indemnified parties and that all such fees and expenses shall be reimbursed as they are incurred. Such firm shall be designated in writing by the Representatives, in the case of parties indemnified pursuant to Section 8(a), and by the Company, in the case of parties indemnified pursuant to Section 8(b). The indemnifying party shall not be liable for any settlement of any proceeding effected without its written consent, but if settled with such consent or if there be a final judgment for the plaintiff, the indemnifying party agrees to indemnify the indemnified party from and against any loss or liability by reason of such settlement or judgment. Notwithstanding the foregoing sentence, if at any time an indemnified party shall have requested an indemnifying party to reimburse the indemnified party for fees and expenses of counsel as contemplated by the second and third sentences of this paragraph, the indemnifying party agrees that it shall be liable for any settlement of any proceeding effected without its written consent if (i) such settlement is entered into more than 30 days after receipt by such indemnifying party of the aforesaid request and (ii) such indemnifying party shall not have reimbursed the indemnified party in accordance with such request prior to the date of such settlement. No indemnifying party shall, without the prior written consent of the indemnified party, effect any settlement of any pending or threatened proceeding in respect of which any indemnified party is or could have been a party and indemnity could have been sought hereunder by such indemnified party, unless such settlement includes an unconditional release of such indemnified party from all liability on claims that are the subject matter of

such proceeding and does not include a statement as to or an admission of fault, culpability or a failure to act by or on behalf of any indemnified party.

(d) To the extent the indemnification provided for in Section 8(a) or 8(b) is unavailable to an indemnified party or insufficient in respect of any losses, claims, damages or liabilities referred to therein, then each indemnifying party under such paragraph, in lieu of indemnifying such indemnified party thereunder, shall contribute to the amount paid or payable by such indemnified party as a result of such losses, claims, damages or liabilities (i) in such proportion as is appropriate to reflect the relative benefits received by the Company on the one hand and the Underwriters on the other hand from the offering of the Shares or (ii) if the allocation provided by clause 8(d)(i) above is not permitted by applicable law, in such proportion as is appropriate to reflect not only the relative benefits referred to in clause 8(d)(i) above but also the relative fault of the Company on the one hand and of the Underwriters on the other hand in connection with the statements or omissions that resulted in such losses, claims, damages or liabilities, as well as any other relevant equitable considerations. The relative benefits received by the Company on the one hand and the Underwriters on the other hand in connection with the offering of the Shares shall be deemed to be in the same respective proportions as the net proceeds from the offering of the Shares (before deducting expenses) received by the Company and the total underwriting discounts and commissions received by the Underwriters, in each case as set forth in the table on the cover of the Prospectus, bear to the aggregate Public Offering Price of the Shares. The relative fault of the Company on the one hand and the Underwriters on the other hand shall be determined by reference to, among other things, whether the untrue or alleged untrue statement of a material fact or the omission or alleged omission to state a material fact relates to information supplied by the Company or by the Underwriters and the parties' relative intent, knowledge, access to information and opportunity to correct or prevent such statement or omission. The Underwriters' respective obligations to contribute pursuant to this Section 8 are several in proportion to the respective number of Shares they have purchased hereunder, and not joint.

(e) The Company and the Underwriters agree that it would not be just or equitable if contribution pursuant to this Section 8 were determined by *pro rata* allocation (even if the Underwriters were treated as one entity for such purpose) or by any other method of allocation that does not take account of the equitable considerations referred to in Section 8(d). The amount paid or payable by an indemnified party as a result of the losses, claims, damages and liabilities referred to in Section 8(d) shall be deemed to include, subject to the limitations set forth above, any legal or other expenses reasonably incurred by such indemnified party in connection with investigating or defending any such action or claim. Notwithstanding the provisions of this Section 8, no Underwriter shall be required to contribute any amount in excess of the amount by which the total price at which the Shares underwritten by it and distributed to the public were offered to the public exceeds the amount of any damages that such Underwriter has otherwise been required to pay by reason of such untrue or alleged untrue statement or omission or alleged omission. No person guilty of fraudulent misrepresentation (within the meaning of Section 11(f) of the Securities Act) shall be entitled to contribution from any person who was not guilty of such fraudulent misrepresentation. The remedies

provided for in this Section 8 are not exclusive and shall not limit any rights or remedies which may otherwise be available to any indemnified party at law or in equity.

(f) The indemnity and contribution provisions contained in this Section 8 and the representations, warranties and other statements of the Company contained in this Agreement shall remain operative and in full force and effect regardless of (i) any termination of this Agreement, (ii) any investigation made by or on behalf of any Underwriter, any person controlling any Underwriter or any affiliate of any Underwriter or by or on behalf of the Company, its officers or directors or any person controlling the Company and (iii) acceptance of and payment for any of the Shares.

9. *Termination*. The Underwriters may terminate this Agreement by notice given by you to the Company, if after the execution and delivery of this Agreement and prior to the Closing Date (i) trading generally shall have been suspended or materially limited on, or by, as the case may be, any of the New York Stock Exchange, the NYSE MKT, the NASDAQ Global Market, the Chicago Board of Options Exchange, the Chicago Mercantile Exchange or the Chicago Board of Trade, (ii) trading of any securities of the Company shall have been suspended on any exchange or in any over-the-counter market, (iii) a material disruption in securities settlement, payment or clearance services in the United States shall have occurred, (iv) any moratorium on commercial banking activities shall have been declared by Federal or New York State authorities or (v) there shall have occurred any outbreak or escalation of hostilities, or any change in financial markets or any calamity or crisis that, in your judgment, is material and adverse and which, singly or together with any other event specified in this clause (v), makes it, in your judgment, impracticable or inadvisable to proceed with the offer, sale or delivery of the Shares on the terms and in the manner contemplated in the Time of Sale Prospectus or the Prospectus.

10. *Effectiveness; Defaulting Underwriters*. This Agreement shall become effective upon the execution and delivery hereof by the parties hereto.

If, on the Closing Date or an Option Closing Date, as the case may be, any one or more of the Underwriters shall fail or refuse to purchase Shares that it has or they have agreed to purchase hereunder on such date, and the aggregate number of Shares which such defaulting Underwriter or Underwriters agreed but failed or refused to purchase is not more than one-tenth of the aggregate number of the Shares to be purchased on such date, the other Underwriters shall be obligated severally in the proportions that the number of Firm Shares set forth opposite their respective names in Schedule I bears to the aggregate number of Firm Shares set forth opposite the names of all such non-defaulting Underwriters, or in such other proportions as you may specify, to purchase the Shares which such defaulting Underwriter or Underwriters agreed but failed or refused to purchase on such date; *provided* that in no event shall the number of Shares that any Underwriter has agreed to purchase pursuant to this Agreement be increased pursuant to this Section 10 by an amount in excess of one-ninth of such number of Shares without the written consent of such Underwriter. If, on the Closing Date, any Underwriter or Underwriters shall fail or refuse to purchase Firm Shares and the aggregate number of Firm Shares with respect to which such default occurs is more than

one-tenth of the aggregate number of Firm Shares to be purchased on such date, and arrangements satisfactory to you and the Company for the purchase of such Firm Shares are not made within 36 hours after such default, this Agreement shall terminate without liability on the part of any non-defaulting Underwriter or the Company. In any such case either you or the Company shall have the right to postpone the Closing Date, but in no event for longer than seven days, in order that the required changes, if any, in the Registration Statement, in the Time of Sale Prospectus, in the Prospectus or in any other documents or arrangements may be effected. If, on an Option Closing Date, any Underwriter or Underwriters shall fail or refuse to purchase Additional Shares and the aggregate number of Additional Shares with respect to which such default occurs is more than one-tenth of the aggregate number of Additional Shares to be purchased on such Option Closing Date, the non-defaulting Underwriters shall have the option to (i) terminate their obligation hereunder to purchase the Additional Shares to be sold on such Option Closing Date or (ii) purchase not less than the number of Additional Shares that such non-defaulting Underwriters would have been obligated to purchase in the absence of such default. Any action taken under this paragraph shall not relieve any defaulting Underwriter from liability in respect of any default of such Underwriter under this Agreement.

If this Agreement shall be terminated by the Underwriters, or any of them, because of any failure or refusal on the part of the Company to comply with the terms or to fulfill any of the conditions of this Agreement, or if for any reason the Company shall be unable to perform its obligations under this Agreement, the Company will reimburse the Underwriters or such Underwriters as have so terminated this Agreement with respect to themselves, severally, for all out-of-pocket expenses (including the fees and disbursements of their counsel) reasonably incurred by such Underwriters in connection with this Agreement or the offering contemplated hereunder.

11. *Entire Agreement.* (a) This Agreement, together with any contemporaneous written agreements and any prior written agreements (to the extent not superseded by this Agreement) that relate to the offering of the Shares, represents the entire agreement between the Company and the Underwriters with respect to the preparation of any preliminary prospectus, the Time of Sale Prospectus, the Prospectus, the conduct of the offering, and the purchase and sale of the Shares.

(b) The Company acknowledges that in connection with the offering of the Shares: (i) the Underwriters have acted at arm's length, are not agents of, and owe no fiduciary duties to, the Company or any other person, (ii) the Underwriters owe the Company only those duties and obligations set forth in this Agreement and prior written agreements (to the extent not superseded by this Agreement), if any, and (iii) the Underwriters may have interests that differ from those of the Company. The Company waives to the full extent permitted by applicable law any claims it may have against the Underwriters arising from an alleged breach of fiduciary duty in connection with the offering of the Shares.

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12. *Counterparts*. This Agreement may be signed in two or more counterparts, each of which shall be an original, with the same effect as if the signatures thereto and hereto were upon the same instrument.

13. *Applicable Law*. This Agreement shall be governed by and construed in accordance with the internal laws of the State of New York.

14. *Headings*. The headings of the sections of this Agreement have been inserted for convenience of reference only and shall not be deemed a part of this Agreement.

15. *Notices*. All communications hereunder shall be in writing and effective only upon receipt and if to the Underwriters shall be delivered, mailed or sent to you in care of Morgan Stanley & Co. LLC, 1585 Broadway, New York, New York 10036, Attention: Equity Syndicate Desk, with a copy to the Legal Department; and if to the Company shall be delivered, mailed or sent to 500 Boylston Street, 11th Floor, Boston, Massachusetts 02116, attention of the Legal Department.

[*Remainder of page intentionally left blank*]

Very truly yours,

RHYTHM PHARMACEUTICALS, INC.

By: ______________________________
Name: Keith Gottesdiener
Title: Chief Executive Officer

[*Signature Page to Underwriting Agreement*]

Accepted as of the date hereof

Morgan Stanley & Co. LLC
Merrill Lynch, Pierce, Fenner & Smith
Incorporated
Cowen and Company, LLC

Acting severally on behalf of themselves and the several Underwriters named in Schedule I hereto.

By: Morgan Stanley & Co. LLC

By: ______________________________
Name:
Title:

By: Merrill Lynch, Pierce, Fenner & Smith
Incorporated

By: ______________________________
Name:
Title:

By: Cowen and Company, LLC

By: ______________________________
Name:
Title:

[*Signature Page to Underwriting Agreement*]

SCHEDULE I

Underwriter	Number of Firm Shares To Be Purchased
Morgan Stanley & Co. LLC	
Merrill Lynch, Pierce, Fenner & Smith Incorporated	
Cowen and Company, LLC	
Needham & Company, LLC	
Total:	

SCHEDULE II

Time of Sale Prospectus

1. Preliminary Prospectus issued [date]

2. [identify all free writing prospectuses filed by the Company under Rule 433(d) of the Securities Act]

3. [free writing prospectus containing a description of terms that does not reflect final terms, if the Time of Sale Prospectus does not include a final term sheet]

4. [orally communicated pricing information such as price per share and size of offering if a Rule 134 pricing term sheet is used at the time of sale instead of a pricing term sheet filed by the Company under Rule 433(d) as a free writing prospectus]

SCHEDULE III

Schedule of Written Testing-the-Waters Communication

[list all Written Testing-the-Waters Communication]

SCHEDULE IV

New Enterprise Associates 13, L.P.

NEA Ventures 2009 Limited Partnership

Third Rock Ventures, L.P.

MPM BioVentures V, L.P.

MPM Asset Management Investors BV5 LLC

Keith Gottesdiener

Hunter Smith

Nithya Desikan

Lex H.T. Van der Ploeg

Fred T. Fiedorek

Simon Kelner

Nithya Desikan

Ed Mathers

Neil Exter

Todd Foley

Christopher Jean

David McGirr

David Meeker

EXHIBIT A-1

[FORM OF OPINION OF COMPANY COUNSEL]

EXHIBIT A-2

[FORM OF OPINION OF SPECIAL REGULATORY COUNSEL]

EXHIBIT A-3

[FORM OF OPINION OF SPECIAL INTELLECTUAL PROPERTY COUNSEL]

EXHIBIT A-4

[FORM OF OPINION OF SPECIAL INTELLECTUAL PROPERTY COUNSEL]

EXHIBIT B

[FORM OF LOCK-UP LETTER]

FORM OF WAIVER OF LOCK-UP

, 20

[Name and Address of
Officer or Director
Requesting Waiver]

Dear Mr./Ms. [Name]:

This letter is being delivered to you in connection with the offering by Rhythm Pharmaceuticals, Inc. (the “**Company**”) of shares of common stock, $0.001 par value (the “**Common Stock**”), of the Company and the lock-up letter dated [ ], 2018 (the “Lock-up Letter”), executed by you in connection with such offering, and your request for a [waiver] [release] dated , 20 , with respect to shares of Common Stock (the “**Shares**”).

Morgan Stanley & Co. LLC, Merrill Lynch, Pierce, Fenner & Smith Incorporated and Cowen and Company, LLC hereby agree to [waive] [release] the transfer restrictions set forth in the Lock-up Letter, but only with respect to the Shares, effective , 20 ; provided, however, that such [waiver] [release] is conditioned on the Company announcing the impending [waiver] [release] by press release through a major news service at least two business days before effectiveness of such [waiver] [release]. This letter will serve as notice to the Company of the impending [waiver] [release].

Except as expressly [waived] [released] hereby, the Lock-up Letter shall remain in full force and effect.

Very truly yours,

Morgan Stanley & Co. LLC
Merrill Lynch, Pierce, Fenner & Smith
Incorporated

Cowen and Company, LLC
Acting severally on behalf of themselves and the several Underwriters named in Schedule I hereto

By: ______________________________
Name:
Title:

cc: Company

Exhibit 5.1

June 18, 2018

Rhythm Pharmaceuticals, Inc.
500 Boylston Street, 11th Floor
Boston, MA 02116

Re: Form S-1 Registration Statement

Ladies and Gentlemen:

We have acted as counsel to Rhythm Pharmaceuticals, Inc., a Delaware corporation (the "Company"), in connection with the filing of a registration statement on Form S-1, initially filed on June 18, 2018 (the "Registration Statement") by the Company with the Securities and Exchange Commission (the "Commission") pursuant to the Securities Act of 1933, as amended (the "Securities Act").

The Registration Statement relates to the proposed offering and sale of up to $172,500,000 of shares of common stock of the Company, par value $0.001 per share (the "Shares"), which includes up to $22,500,000 of the Shares subject to the underwriters' over-allotment option described in the Registration Statement.

This opinion is being furnished in connection with the requirements of Item 601(b)(5) of Regulation S-K under the Act, and no opinion is expressed herein as to any matter pertaining to the contents of the Registration Statement or the related prospectus (the "Prospectus"), other than as expressly stated herein with respect to the issuance of the Shares.

As such counsel, we have examined such matters of fact and questions of law as we have considered appropriate for purposes of this letter. With your consent, we have relied upon certificates and other assurances of officers of the Company and others as to factual matters without having independently verified such factual matters. We are opining herein as to the General Corporation Law of the State of Delaware (the "DGCL"), and we express no opinion with respect to any other laws.

Subject to the foregoing and the other matters set forth herein, it is our opinion that, as of the date hereof, when the Shares shall have been duly registered on the books of the transfer agent and registrar therefor in the name or on behalf of the purchasers and have been issued by the Company against payment therefor in the circumstances contemplated by the form of underwriting agreement most recently filed as an exhibit to the Registration Statement, the issue and sale of the Shares will have been duly authorized by all necessary corporate action of the Company, and the Shares will be validly issued, fully paid, and nonassessable. In rendering the foregoing opinion, we have assumed that the Company will comply with all applicable notice requirements regarding uncertificated shares provided in the DGCL.

This opinion is for your benefit in connection with the Registration Statement and may be relied upon by you and by persons entitled to rely upon it pursuant to the applicable provisions of the Act. We consent to your filing this opinion as an exhibit to the Registration Statement and to the reference to our firm in the Prospectus under the heading "Legal Matters." In giving such consent, we do not thereby admit that we are in the category of persons whose consent is required under Section 7 of the Act or the rules and regulations of the Commission thereunder.

Very truly yours,

/s/ MORGAN, LEWIS & BOCKIUS LLP

Exhibit 10.17

RHYTHM PHARMACEUTICALS, INC.

FIRST AMENDMENT
TO THE
2017 EMPLOYEE STOCK PURCHASE PLAN

This FIRST AMENDMENT (this "Amendment") to the 2017 Employee Stock Purchase Plan (the "Plan"), of Rhythm Pharmaceuticals, Inc. (the "Company"), is being adopted by the Compensation Committee of the Board of Directors, by unanimous written consent in lieu of a special meeting dated as of April 19, 2018. The Plan is hereby amended as follows:

1. Section 6.1 of the Plan hereby is amended and restated in its entirety as follows:

> 6.1 Plan Periods. The Initial Plan Period shall commence on June 1, 2018 and continue for six months. After the Initial Plan Period, there will be two consecutive six-month Plan Periods during each twelve-month period thereafter, with the first six-month Plan Period beginning on December 1 and ending on the immediately following May 31, and the second six-month Plan Period beginning on June 1 and ending on the immediately following November 30 unless otherwise determined by the Committee. Notwithstanding the foregoing, the Chief Executive Officer and/or Chief Financial Officer of the Company shall have the authority, in their sole discretion, to select different dates for the start date of the Initial Plan Period and the subsequent Plan Periods.

Except to the extent amended hereby, all of the terms, provisions and conditions set forth in the Plan are hereby ratified and confirmed and shall remain in full force and effect. The Plan and this Amendment shall be read and construed together as a single instrument.

[*End of Document*]

Exhibit 21.1

Entity	State of Formation
Rhythm Securities Corp.	Massachusetts

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the reference to our firm under the caption “Experts” and to the use of our report dated March 12, 2018 (except Note 12, as to which the date is June 11, 2018) in the Registration Statement (Form S-1) and the related Prospectus of Rhythm Pharmaceuticals, Inc. for the registration of shares of its common stock.

/s/ Ernst & Young LLP

Boston, Massachusetts
June 18, 2018