UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2019
OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to
Commission file number 001-38223

RHYTHM PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**46-2159271**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)

222 Berkeley Street
12th Floor
Boston, MA 02116
(Address of principal executive offices)
(Zip Code)

(857) 264-4280
(Registrant's telephone number, including area code)

N/A
(Former name, former address and former fiscal year, if changed since last report)

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.001 par value per share	RYTM	The Nasdaq Stock Market LLC (Nasdaq Global Market)

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15 (d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (of this chapter)during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, 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.

Large accelerated filer ☐	Accelerated filer ☒
Non-accelerated filer ☐	Smaller reporting company ☐
	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. ☒

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒.

The aggregate market value of the Common Stock held by non-affiliates of the registrant was approximately $569.4 million, based on the closing price of the registrant's Common Stock on June 28, 2019, the last business day of the registrant's most recently completed second fiscal quarter.

There were 44,058,909 shares of Common Stock outstanding as of February 28, 2020.

DOCUMENTS INCORPORATED BY REFERENCE

The registrant intends to file a definitive proxy statement pursuant to Regulation 14A within 120 days of the end of the fiscal year ended December 31, 2019. Portions of such definitive proxy statement are incorporated by reference into Part III of this Annual Report on Form 10-K.

RHYTHM PHARMACEUTICALS, INC.
ANNUAL REPORT ON FORM 10-K
For the Year Ended December 31, 2019

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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K, or this Annual Report, contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, and is subject to the "safe harbor" created by those sections. Any statements about our expectations, beliefs, plans, objectives, assumptions or future events or performance are not historical facts and may be forward-looking. Some of the forward-looking statements can be identified by the use of forward-looking terms such as "anticipates," "believes," "could," "estimates," "expects," "intends," "may," "might," "likely," "plans," "potential," "predicts," "projects," "seeks," "should," "target," "will," "would," or similar expressions and the negatives of those terms include forward-looking statements that involve risks and uncertainties. Forward-looking statements include, but are not limited to, statements regarding our expectations regarding timing and enrollment of clinical trials, timing for the announcement of data and filing of regulatory applications, expectations regarding our indications for our product candidates, expectations regarding our strategy and commercial sales, expectations regarding prevalence, expectations regarding our patient identification efforts, anticipated expenses, the sufficiency of cash, and the impact of accounting pronouncements. We cannot guarantee future results, levels of activity, performance or achievements, and you should not place undue reliance on our forward-looking statements. Our actual results may differ significantly from the results discussed in the forward-looking statements. Factors that might cause such a difference include, but are not limited to, those set forth in "Item 1A. Risk Factors" and elsewhere in this Annual Report. Except as may be required by law, we have no plans to update our forward-looking statements to reflect events or circumstances after the date of this Annual Report. We caution readers not to place undue reliance upon any such forward-looking statements, which speak only as of the date made.

Unless the content requires otherwise, references to "Rhythm Pharmaceuticals," "Rhythm," "the Company," "we," "our," and "us," in this Annual Report refer to Rhythm Pharmaceuticals, Inc. and its subsidiaries.

PART I

Item 1. Business

Overview

We are a late-stage biopharmaceutical company focused on the development and commercialization of therapeutics for the treatment of rare genetic disorders which are characterized by severe, early-onset obesity and an unrelenting hunger or hyperphagia. Our lead product candidate is setmelanotide, a potent melanocortin-4 receptor, or MC4R, agonist 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 MC4R pathway deficiencies. MC4R 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.

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 MC4R 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 MC4R pathway.

We plan to complete and submit new drug applications, or NDAs, for pro-opiomelanocortin, or POMC, deficiency obesity and leptin receptor, or LEPR, deficiency obesity in the first quarter of 2020. We recently reported positive topline Phase 3 data demonstrating a statistically significant and clinically meaningful impact on weight loss and hunger in patients with POMC deficiency obesity and LEPR deficiency obesity. Additionally, we completed enrollment in the pivotal cohort in December 2019 in a Phase 3 trial evaluating setmelanotide for the treatment of both severe hunger and obesity in individuals living with Bardet-Biedl syndrome, or BBS, or Alström syndrome. We plan to report topline data from this pivotal trial in the fourth quarter of 2020 or early in the first quarter of 2021.

In clinical trials of setmelanotide in these four genetic disorders of extreme and unrelenting appetite and obesity, subjects experienced dramatic reductions in 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 MC4R in the leptin melanocortin pathways. The Breakthrough Therapy designation currently covers POMC deficiency obesity, LEPR deficiency obesity, BBS and Alström syndrome.

We are working to expand the potential market for setmelanotide beyond these first four indications through a robust series of genetic sequencing efforts and our exploratory Phase 2 Basket Study. We have been collaborating with partners to advance its own initiatives to sequence individuals living with early-onset, severe obesity to uncover additional rare genetic disorders of obesity, and develop a better understanding of those disorders. In September 2019, we reported on sequencing samples from 13,567 individuals (collected as of June 2019) with severe obesity, and those samples have yielded 11.7%, or 1,584 genetically-identified individuals, who have a rare genetic variant of the MC4R pathway and who may be eligible for inclusion in our Phase 2 Basket Study or our pivotal Phase 3 trials. Inclusive of these results, our sequencing programs have now sequenced over 25,000 severely obese individuals. We plan to update results from our sequencing activity in 2020.

Additionally, we are assessing setmelanotide in POMC epigenetic disorders, leptin deficiency obesity, or LEP, and Carboxypeptidase E deficiency obesity, or CPE, as part of investigator-initiated protocols within the Phase 2 Basket Study. For patients who may have any of these disorders, hyperphagia and obesity can have significant health consequences for which there is currently no approved treatment. For POMC or LEPR heterozygous deficiency obesity, which we also refer to as HET obesity, we reported initial, preliminary results from these trials in June 2018, and provided a further update in March 2019. We expect to report additional data in this indication and at least one other indication in 2020.

In addition to our development of setmelanotide, we also are developing a second investigational asset, RM-853. RM-853 is an 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 acquired exclusive, worldwide rights from Takeda Pharmaceutical Company Limited, or Takeda, in April 2018 to develop and commercialize this asset, which Takeda called T-3525770. We anticipate filing an Investigational New Drug application, or IND, for RM-853 with the FDA in 2020.

Our Strategy

Our goal is to be a leader in developing and commercializing targeted therapies for genetic deficiencies that result in severe obesity and hyperphagia. The key components of our strategy are:

- **Rapidly develop setmelanotide for rare genetic disorders of obesity caused by MC4R 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 MC4R pathway. We are focusing setmelanotide clinical development on monogenic upstream genetic defects in which obesity is life-threatening but where the downstream MC4R pathway is fully functional. We are currently evaluating setmelanotide for the treatment of upwards of 10 rare genetic disorders of obesity. We believe that focusing on these rare conditions with high unmet needs enables us to rapidly develop and commercialize setmelanotide using relatively small clinical trials with increased potential for clinical and regulatory success.

- **Advance setmelanotide for POMC deficiency obesity and LEPR deficiency obesity as our first indications in upstream MC4R pathway deficiencies.** We plan to complete and submit NDAs for POMC deficiency obesity and LEPR deficiency obesity in the first quarter of 2020 and follow that with submission of our Marketing Authorization Application for the same to the European Medicines Association.

- **Advance setmelanotide for Bardet-Biedl syndrome and Alström syndrome as our second set of indications in upstream MC4R pathway deficiencies.** We completed enrollment of the pivotal cohort in

December 2019 in a Phase 3 trial evaluating setmelanotide for the treatment of insatiable hunger and severe obesity in individuals living with BBS or Alström syndrome. We plan to report topline data in the fourth quarter of 2020 or early in the first quarter of 2021.

- **Expand setmelanotide development to additional MC4R pathway deficiencies, including POMC or LEPR heterozygous deficiency obesity, steroid receptor coactivator 1, or SRC1, deficiency obesity, SH2b adapter protein 1, or SH2B1, deficiency obesity, MC4R deficiency obesity, Smith-Magenis syndrome and more.** We believe we can leverage our experience with and mechanistic understanding of the MC4R pathway to advance development of setmelanotide for other upstream MC4R pathway deficiencies. Our Phase 2 Basket Study enables us to study a variety of different indications or patient populations administratively in one protocol, though each population is enrolled and analyzed separately. This enables us to study more indications for the same compound with a reduced administrative and regulatory burden. We are enrolling patients in multiple cohorts in our Phase 2 Basket Study of setmelanotide for the treatment of several distinct MC4R pathway deficiency obesities. We estimate a combined U.S. prevalence for these indications to be greater than 80,000 patients.

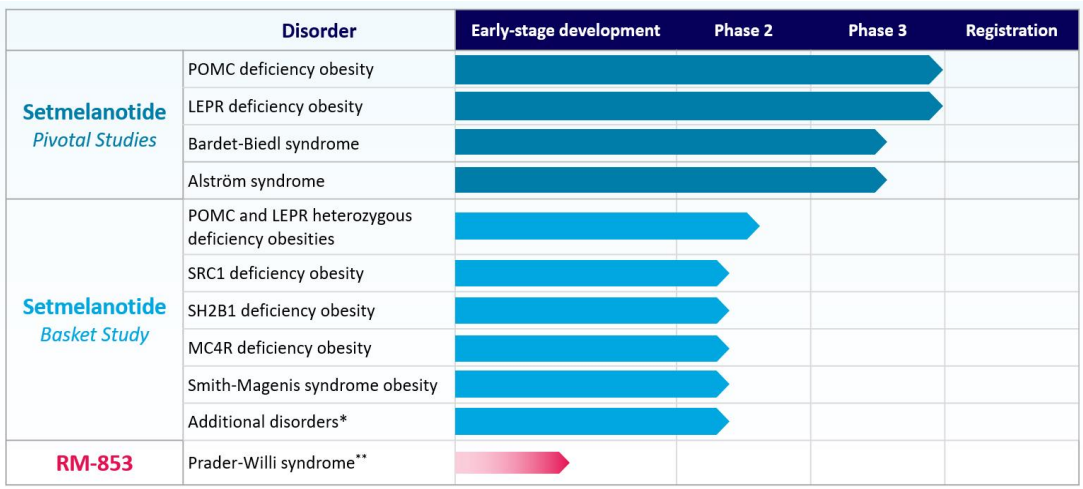
- **Commercialize setmelanotide for rare disease indications in core strategic markets.** We are building upon our clinical development and research expertise in these diseases to further the understanding and identification of patients with rare genetic disorders of obesity in the broader health care community. Our efforts, in combination with our Rhythm-sponsored genotyping initiatives, will help to drive awareness of these disorders; suspicion among patients, providers and caregivers that individuals may be suffering from these disorders; and ultimately, genetic sequencing designed to support improved diagnosis. Through collaborations with key thought leaders, advocacy organizations, patients, and care givers, we will provide critical stakeholder education to build an integrated community dedicated to improving the ultimate treatment of these patients.

  Ultimately, we intend to establish our own commercial sales and marketing organization in the United States and other core strategic markets. We expect that 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 collaborations 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 MC4R pathway deficiencies and the current state of development, as well as the development status of RM-853, our preclinical asset:



** We are currently assessing setmelanotide in additional disorders, including POMC epigenetic disorders and LEP and CPE deficiency obesity, as part of investigator-initiated protocols within the basket study. Given the recent discovery of these rare disorders of the MC4R pathway, there is currently limited or no genetic sequencing or epidemiology data that defines prevalence. However, we believe that these are rare disorders which may be setmelanotide-responsive.*

*** We are currently assessing opportunities to further evaluate setmelanotide in PWS and plans to pursue these in parallel with the development of RM-853.*

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 MC4R 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 characterized at least in part with early-onset, severe obesity and hyperphagia that are the result of genetic defects affecting the MC4R pathway, including BBS, Alström syndrome, POMC or LEPR heterozygous deficiency obesity, SRC1 deficiency obesity, SH2B1 deficiency obesity, MC4R deficiency obesity and Smith Magenis syndrome as well as POMC epigenetic disorders and LEP and CPE deficiency obesities. 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 MC4R pathway. We believe that this approach has the potential to provide dramatic improvements in weight and appetite by restoring lost function in the MC4R pathway.

Obesity Caused by Rare Genetic Deficiencies Affecting the MC4R Pathway

The MC4R 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.

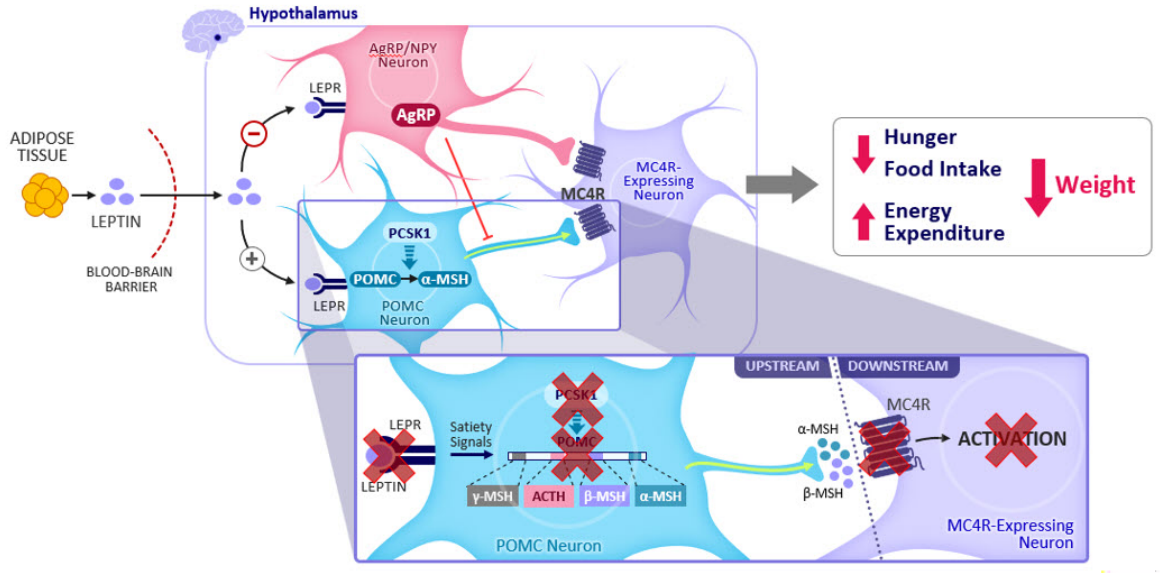
This important hypothalamic, or lower brainstem, pathway has been the focus of extensive investigation for many years, and we have a deep understanding of this mechanism, which is unlike the targets of most other anti-obesity therapies. As a result, we believe we can better predict the efficacy and safety profile expected from modulating this target. The critical role of the MC4R 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 MC4R 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 PCSK1, enzyme, into melanocyte stimulating hormone, or MSH, the natural ligand, or activator, for MC4R. When upstream genetic mutations disrupt this pathway, it can lead to insufficient MC4R activation and 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 MC4R pathway below the genetic defect. In this way, we believe setmelanotide acts as replacement therapy.

The figure below also illustrates some of the genes that are upstream within the MC4R pathway and the potential effect on the activation of the MC4R, which regulates hunger and energy expenditure. We are focused on deficiencies in the genes of this pathway.

Setmelanotide Development Targets: Upstream Deficiencies Affecting the MC4R Pathway



AgRP, agouti-related protein; ARC, arcuate nucleus; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; NPY, neuropeptide Y; PCSK1, proprotein convertase subtilisin/kexin-type 1; POMC, proopiomelanocortin; PVN, paraventricular nucleus of hypothalamus. Reference: Yazdi FT et al. PeerJ. 2015;3:e856.

Epidemiology Estimates of Rare Genetic Disorders of the MC4R Pathway

While obesity is epidemic in the United States and elsewhere, we are focused on rare genetic disorders of obesity, most often characterized by severe, early-onset obesity and unrelenting hunger or hyperphagia. Of the tens of millions of obese individuals in the United States, we estimate that there are approximately 5.7 million individuals whose severe obesity was early-onset[1]. The table below summarizes the indications on which we are focusing for the development of

setmelanotide, including our clinical epidemiology estimates based on the literature and company sequencing data for the addressable patient populations within these indications.

POMC deficiency obesity	~100 – 500 U.S. patients
LEPR deficiency obesity	~500 – 2,000 U.S. patients
Bardet-Biedl syndrome	~2,500 U.S. patients
Alström syndrome	~500 U.S. patients
POMC or LEPR heterozygous deficiency obesity	~20,000 U.S. patients
SRC1 deficiency obesity	~23,000 U.S. patients
SH2B1 deficiency obesity	~24,000 U.S. patients
MC4R deficiency obesity	~10,000* U.S. Patients
Smith Magenis syndrome	~2,400 U.S. patients

* Estimated prevalence of U.S. patients with rescuable variants of the MC4R.

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 Rhythm-derived estimates described above. Estimates are not yet available for POMC epigenetic disorders and LEP and CPE deficiency obesities.

For patients with genetic forms of MC4R pathway deficiencies, the rarity of our target indications means that there is no comprehensive patient registry or other method of establishing with precision the actual number of patients. As a result, we have had to rely on other available sources to derive clinical prevalence estimates for our target indications. In addition, we have internal genetic sequencing results from 13,567 patients with severe obesity that provide another approach to estimating prevalence. 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 MC4R pathway deficiencies based on the following sources and assumptions:

- *POMC Deficiency Obesity.* Our addressable patient population estimate for POMC deficiency obesity is approximately 100 to 500 patients in the United States, with a comparable addressable patient population in Europe. Our estimates are based on:
    - 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 obesity is often unavailable and currently is rarely performed;

[1]These calculations assume a U.S. population of 327 million, of which 1.7% have early-onset, severe obesity (Hales et al in JAMA – April 2018: Trends in Obesity and Severe Obesity Prevalence in US Youth and Adults by Sex and Age, 2007-2008 to 2015-2016);

- our belief, based on discussions with experts in rare diseases, that the number of diagnosed cases could increase several-fold with increased awareness of this deficiency and the availability of new treatments;
- 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
- our internal sequencing yield for POMC deficiency obesity patients (including both POMC and proprotein convertase subtilisin/kexin 1, or PCSK1, gene disorders) of approximately 0.06%.

- *LEPR Deficiency Obesity.* Our addressable patient population estimate for LEPR deficiency obesity is approximately 500 to 2,000 patients in the United States, with a comparable addressable patient population in Europe. Our estimates are based on:
  - epidemiology studies on LEPR deficiency obesity 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 (BMI greater than 40 kg/ m^2) and for severe early onset obese children (99th percentile at ages two to 17 years old);
  - with wider availability of genetic testing expected for LEPR deficiency obesity and increased awareness of new treatments, our belief that up to 40% of patients with these disorders may eventually be diagnosed; and
  - our internal sequencing yield for LEPR deficiency obesity patients of approximately 0.15%.

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 obesity, and (z) our estimated diagnosis rate of up to 40%. In addition, we considered the results of our internal sequencing yields, which support our clinical epidemiology estimates.

- *Bardet-Biedl Syndrome.* Our addressable patient population estimate for BBS 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 BBS 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 patients in the United States. 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 or LEPR Heterozygous Deficiency Obesities, or HET obesity.* Our addressable patient population estimate for patients with high-impact variants (the subset of POMC or LEPR heterozygous patients with loss of function variants such as truncations, frame-shift, and splice variants as well as well-characterized, published missense variants likely to cause loss of function of the MC4R pathway, expected to be most responsive to setmelanotide) is approximately greater than 20,000 patients in the United States, with a comparable addressable patient population in Europe. Our estimates are based on:

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

  - our internal sequencing yield for patients with high-impact variants of approximately 0.7%.

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

- *SRC1 Deficiency Obesity.* Our addressable patient population estimate for SRC1 deficiency obesity is approximately greater than 23,000 patients in the United States. This estimate is based on:

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

  - our internal sequencing yield for SRC1 deficiency obesity patients of approximately 2.5% prior to application of functional and computational filters.

- *SH2B1 Deficiency Obesity.* Our addressable patient population estimate for SH2B1 deficiency obesity is approximately greater than 24,000 patients in the United States. This estimate is based on:

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

  - our internal sequencing yield for SH2B1 deficiency obesity patients of approximately 1.8% prior to application of functional and computational filters.

- *MC4R Deficiency Obesity.* Our addressable patient population estimate for MC4R deficiency obesity is approximately greater than 10,000 patients in the United States. This estimate is based on:

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

  - our internal sequencing yield for MC4R deficiency obesity patients of approximately 2.0% prior to application of functional filters.

- *Smith-Magenis Syndrome.* Our addressable patient population estimate for Smith-Magenis syndrome is approximately greater than 2,400 patients in the United States. This estimate is based on:

  - published prevalence estimates of one in 25,000 in the United States, which projects to approximately 13,000 people in the United States;

- published prevalence estimates that approximately 10% of patients with Smith-Magenis syndrome have RAI1 variants that may affect the MC4R pathway and 90% of patients with Smith-Magenis syndrome have 17p11.2 chromosomal deletions which also may affect the MC4R pathway, of which approximately 67% and 13%, respectively, live with obesity; and

- U.S. Census Bureau figures for total population of adults and children.

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 EU and these estimates are therefore based solely on applying relative population percentages to the Rhythm-derived estimates described above.

We have developed a patient registry for diagnosed patients with POMC deficiency and LEPR deficiency (and other genetic disorders of obesity) which might 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, and suggests that genetic epidemiology estimates of POMC deficiency obesity and LEPR deficiency obesity may be five times higher than clinical epidemiology estimates. 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.

Furthermore, as of September 2019, we collected samples from 13,567 individuals with severe obesity, which yielded 11.7%, or 1,584, genetically-identified individuals with a rare genetic variant of the MC4R pathway and who may be eligible for inclusion in our Phase 2 Basket Study or pivotal Phase 3 clinical trials. Inclusive of these results, our sequencing programs have now sequenced over 25,000 severely obese individuals. We plan to update results from our sequencing activity in 2020. The yields for the indications are outlined above, and in order to establish a prevalence estimate, we applied a rarity filter and functional and/or computational filters to calculate the estimates in the United State population. A rarity filter means the specific variant appears in less than 1% of people, and the functional and computational filters help us focus our estimates based on the highest confidence loss-of-function variants. These genetic sequencing results have identified samples from 29 patients with POMC deficiency obesity and LEPR deficiency obesity, which is consistent with our clinical epidemiology estimates.

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 POMC and LEPR deficiency obesities. However, as the clinical epidemiology estimates tend to be lower, to be conservative, we generally reference the clinical epidemiology figures in our descriptions of our target indications.

Defining the exact genetic variants that result in MC4R pathway disorders is complex. 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.

Obesity Caused by Upstream Genetic Deficiencies Affecting the MC4R Pathway

We have advanced setmelanotide for the treatment of four rare genetic disorders of obesity to Phase 3 clinical trials. We reported positive topline Phase 3 data demonstrating a statistically significant and clinically meaningful impact on weight loss and hunger in patients with POMC deficiency obesity and LEPR deficiency obesity, and we completed enrollment of the pivotal cohort in December 2019 in a Phase 3 trial evaluating setmelanotide for the treatment of insatiable hunger and severe obesity in individuals living with BBS or Alström syndrome. These achievements followed the completion of four positive Phase 2 trials of setmelanotide that provided proof of concept for four upstream MC4R pathway genetic defects in which obesity is life-threatening but the downstream MC4R pathway is fully functional.

POMC Deficiency Obesity

POMC deficiency obesity is an ultra-rare genetic disorder, with severe, early onset obesity, defined here as a 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 increase several-fold 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 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 MC4R 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. 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, through 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 MC4R, but like other deficiencies upstream in the MC4R pathway, lack of signaling at LEPR results in loss of function in the MC4R 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. 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 BBS obesity is approximately 2,500 patients in the United States. BBS is a monogenic disorder that causes severe obesity and hyperphagia as well as vision loss, polydactyly, kidney abnormalities, and other signs and symptoms. For BBS 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 in the hypothalamus is thought to contribute to hyperphagia and obesity in BBS. BBS 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 BBS patient only has one of these defects.

Recent scientific studies identify deficiencies affecting the MC4R pathway as a potential cause of the obesity and hyperphagia associated with BBS and demonstrate that an MC4R agonist can directly impact these symptoms. Studies in mouse models of BBS show that deficiencies in the MC4R pathway contribute to the obesity and hyperphagia in BBS, 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 MC4R agonists is also supported by studies in BBS rodent models, where mice have responded to an MC4R agonist resulting in reduced food intake and body weight. Currently there are no approved or effective therapies for BBS.

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 BBS, recent scientific studies identify genetic deficiencies affecting the MC4R 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 MC4R pathway signaling. While Alström syndrome is less well studied than BBS, the similar pathophysiology of cilia dysfunction and clinical presentation support that deficiencies in the MC4R pathway are implicated in the obesity and hyperphagia observed in Alström syndrome. Currently there are no approved or effective therapies for Alström syndrome.

Other Upstream Genetic Defects in the MC4R Pathway

In addition to the indications which we have advanced into Phase 3 development (POMC deficiency obesity, LEPR deficiency obesity, BBS and Alström syndrome), there are other upstream, MC4R pathway deficiencies for which we believe setmelanotide may function as replacement therapy, including defects that partially modulate POMC activity, such as POMC or LEPR heterozygous deficiency obesity, SRC1 deficiency obesity, SH2B1 deficiency obesity, MC4R deficiency obesity and Smith-Magenis syndrome, as well as POMC epigenetic disorders and LEP and CPE deficiency obesities. Each one of the genes that underlies these indications have strong, well-established, published links to the MC4 receptor pathway, and loss of function in any one of these genes ultimately results in a dysregulation of the pathway that originates due to a decrease in activity of the POMC neuron, and as a consequence, a decrease in MC4 receptor activity, which engenders those kind of canonical clinical presentations of hyperphagia and obesity.

POMC or LEPR heterozygous deficiency obesity

POMC or LEPR heterozygous deficiency obesity 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 20,000 patients in the United States, based on our own genetic sequencing analyses and 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 MC4R 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 MC4R pathway gene heterozygous mutations, including patients with heterozygous mutations in genes such as LEPR and BBS, as well as patients with heterozygous mutations in more than one gene in the MC4R pathway. For simplicity, 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 MC4R 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. There are currently no approved or effective therapies for POMC heterozygous deficiency obesity.

SRC1 deficiency obesity

SRC1 deficiency obesity is a rare genetic disorder that is characterized by early-onset severe obesity, defined here as a BMI of greater than 40 kg/m2, hyperphagia and hyperleptinemia. Patients with SRC1 deficiency obesity are rare. The first academic paper describing SRC1 deficiency obesity, titled, “Steroid receptor coactivator-1 modulates the function of POMC neurons and energy homeostasis” (Yang et al 2019, Nat Comm. 10, Article 1718) was published in 2019 in Nature Communications. In this paper, the authors described how SRC1 variants found in severely obese cases significantly impaired leptin-induced POMC expression. SRC1 deficiency obesity is an autosomal dominant disorder, meaning that heterozygote loss of the SRC1 gene (just one gene copy) can be sufficient to give rise to obesity and hyperphagia.

The SRC1 protein has been shown to have direct links to the MC4R pathway. Specifically, SRC1 is a transcriptional coactivator that has links to both the leptin receptor and to POMC. When the leptin receptor is activated, SRC1 through a cascade of events itself is activated and then goes on to drive the expression of POMC, such that in individuals who have heterozygote loss of function mutations in their SRC1 genes, there's insufficient leptin receptor activation of the MC4 receptor pathway, decreased POMC expression, which decreases the amount of available MSH to reactivate the MC4 receptor, consequentially resulting in that decreased activity that drives the hyperphagia and obesity in these individuals. Based on our sequencing efforts, we estimate that there are more than 23,300 people in the United States living with SRC1 deficiency obesity.

SH2B1 deficiency obesity

SH2B1 deficiency obesity is a rare genetic disorder that is characterized by early-onset severe obesity, defined here as a BMI of greater than 40 kg/m^2, hyperphagia and hyperinsulinemia. In addition to early-onset severe obesity and hyperphagia, other clinical characteristics associated with SH2B1 deficiency obesity are insulin resistance and reduced final height Patients with SH2B1 deficiency obesity are rare. Deficiency in SH2B1 can arise through either DNA variants in the SH2B1 gene or through chromosomal deletions (chromosome 16) that encompass the SH2B1 gene. In both cases, dysfunction/loss of only one copy of the SH2B1 gene is sufficient to give rise to obesity and hyperphagia.

The SH2B1 protein has been shown to have direct links to the MC4R-pathway. Specifically, SH2B1 is an adapter protein that amplifies the signal coming through the leptin receptor. In individuals who carry heterozygote loss of function mutations in SH2B1 or a chromosomal deletion that remove the SH2B1 from the chromosome, individuals have insufficient leptin receptor activity activation of their MC4 receptor pathway. This gives rise to a well-documented form of severe early-onset obesity and hyperphagia. Based on our sequencing efforts and data from published literature, we estimate that there are more than 24,000 people in the United States living with SH2B1 deficiency obesity.

MC4 receptor deficiency obesity

MC4R deficiency obesity may arise due to heterozygote loss of function mutations in the MC4 receptor gene itself, and this is one of the most well-known and most prevalent forms of monogenic severe early-onset 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.

Based on a comprehensive ongoing biochemical screening study, we believe there is an opportunity for setmelanotide in a very defined subset of this broader population, specifically those individuals who carry MC4 receptor loss of function variants that can be rescued by setmelanotide (e.g. are not responsive to the endogenous ligand MSH, but do respond normally to setmelanotide). Based on our sequencing efforts, we estimate that there are approximately 10,000 people in the United States living with MC4R deficiency obesity that may be addressable by setmelanotide.

Smith-Magenis syndrome

Smith-Magenis syndrome is a developmental disorder that affects many parts of the body. The major features of this condition include mild to moderate intellectual disability, delayed speech and language skills, distinctive facial features, sleep disturbances, behavioral problems, and in some cases, adolescent-onset obesity and hyperphagia. Now it arises due to loss of function mutations or chromosomal deletions that ablate the function of a gene called RAI1. RAI1 is a transcription factor that's been shown to affect the expression of several MC4 receptor pathway genes, including POMC itself. As a result, we believe that hyperphagia and obesity found with Smith-Magenis syndrome is likely caused by an overall decrease in the activity of the MC4 receptor pathway.

Smith-Magenis syndrome affects at least 1 in 25,000 individuals worldwide, although many researchers believe that many people with this condition are not diagnosed, and that prevalence could be closer to 1 in 15,000 individuals, according the National Institutes of Health. We estimate that approximately 2,400 individuals with Smith-Magenis syndrome have severe obesity and hyperphagia that may be addressable with setmelanotide.

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. There are currently no approved or effective therapies for these disorders.

Other MC4R Disorders

Based on setmelanotide's biochemical structure and mechanism of action, we believe setmelanotide has the potential to serve as replacement therapy for other rare genetic disorders of obesity which have pathophysiology upstream of the MC4R receptor. We are conducting research activities to study which potential disorders tied to the pathway may benefit from setmelanotide therapy. Our basket study protocols, which enable enrollment of new populations with disorders tied to the pathway, allow us to study new potential indications without the administrative and regulatory burden of initiating a separate clinical study de novo for each new indication.

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 MC4R 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 focused on identifying people with early-onset obesity that may be caused by certain rare genetic variants. We support several initiatives to expand the diagnosis of genetic obesity, including a genotyping study called GO-ID, a sponsored genetic testing program called Uncovering Rare Obesity, and a patient registry called TEMPO. The objective of GO-ID is to develop a screening algorithm for selecting patients to be genotyped and identified with POMC deficiency obesity and LEPR deficiency obesity, and to guide further genotyping efforts. Uncovering Rare Obesity is designed to expand the reach of genetic testing for patients with early-onset, severe obesity beyond academic settings to community physicians and their patients. TEMPO is a commitment to understanding the ongoing impact and burden of disease on patients and their caregivers. This registry is intended to facilitate enhanced understanding of these conditions in the medical community and builds upon ongoing collaborations with existing patient registries in syndromic conditions such as BBS.

In addition, we have an ongoing effort to broaden the understanding of the genetics of obesity through sequencing analyses. In September 2019, we presented data from 13,567 sequenced patient samples of obese individuals collected as of June 2019 through GO-ID, Uncovering Rare Obesity and from third-party genetic databases. We are also conducting genetic obesity epidemiology analysis of MC4R pathway genetic defects in a large representative sample of the U.S. population. 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 MC4R pathway and its potential impact on obesity, showing that the cumulative allele burden, or number of mutations along the MC4R 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 MC4R 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, BBS, Alström syndrome, POMC heterozygous deficiency obesity, or POMC epigenetic disorders. Bariatric surgery is not an option in patients with upstream defects in the MC4R pathway who have severe obesity and hyperphagia.

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

Setmelanotide is a potent 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 MC4R pathway deficiencies, and we have initiated a combined Phase 3 clinical trial in two additional rare genetic disorders. We also have an ongoing Phase 2 clinical trial in several other MC4R pathway disorders. MC4R modulates a key pathway in humans that regulates energy homeostasis and food intake.

The critical role of the MC4R 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. Setmelanotide is a peptide that retains the specificity and functionality of the naturally occurring hormone that activates MC4R, with demonstrated efficacy and little, if any, signal of increases in blood pressure. In total, approximately 450 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 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 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.

Clinical Development in Rare Genetic Disorders of Obesity Caused by MC4R Pathway Deficiencies

Setmelanotide is currently being evaluated in three Phase 3 trials: one trial evaluating efficacy and safety in POMC deficiency obesity, one in LEPR deficiency obesity and one trial that combines BBS and Alström syndrome. We recently reported positive topline Phase 3 data demonstrating a statistically significant and clinically meaningful effect on weight loss and hunger endpoints in patients with POMC deficiency obesity and LEPR deficiency obesity, and we completed enrollment of the pivotal cohort in December 2019 in a Phase 3 trial evaluating setmelanotide for the treatment of insatiable hunger and severe obesity in individuals living with BBS or Alström syndrome. We also are enrolling patients in multiple cohorts in our Phase 2 Basket Study of setmelanotide for the treatment of MC4R pathway deficiency obesities, including POMC or LEPR heterozygous deficiency obesity, SRC1 deficiency obesity, SH2B1 deficiency obesity, MC4R deficiency obesity and Smith Magenis syndrome. Additionally, we are assessing setmelanotide in POMC epigenetic disorders and LEP and CPE deficiency obesities.

Pivotal Phase 3 clinical trials evaluating setmelanotide in POMC and LEPR deficiency obesities

In August 2019, we reported positive topline Phase 3 data demonstrating a statistically significant and clinically meaningful impact on weight loss and hunger in patients with POMC deficiency obesity and LEPR deficiency obesity. Both studies met their primary endpoints and all key secondary endpoints, demonstrating a statistically significant and clinically meaningful effect on weight loss and reductions in insatiable hunger, or hyperphagia, in patients with POMC and LEPR deficiency obesities.

Eight of 10 patients with POMC deficiency obesity achieved the primary endpoint of greater than 10% weight loss over approximately one year ($p<0.0001$). The mean reduction from baseline in body weight for POMC deficiency obesity patients was -25.4% ($p<0.0001$), and the mean reduction from baseline in most hunger rating for POMC deficiency obesity patients was -27.8% ($p=0.0005$). In addition, 50% of the POMC deficiency obesity patients in the trial met or exceeded a 25% improvement in self-reported hunger scores ($p=0.0004$). Mean weight loss for these patients was 31.9 kg, or 70.2 pounds, over one year on therapy.

POMC Phase 3 Topline			
80% p<0.0001	**-25.4%** p<0.0001	**-27.8%** p=0.0005	**31.9kg 70.2lbs**
>10% weight loss	mean weight reduction	mean hunger score reduction	mean weight loss in 1 year

Five of 11 patients with LEPR deficiency obesity achieved the primary endpoint of greater than 10% weight loss over one year (p=0.0001). The mean reduction from baseline in body weight for LEPR deficiency obesity patients was -12.5% (p<0.0001), and the mean reduction from baseline in most hunger rating for LEPR deficiency obesity patients was -41.9% (p<0.0001). In addition, 72.7% of the LEPR deficiency obesity patients in the trial met or exceeded a 25% improvement in self-reported hunger scores (p<0.0001). Mean weight loss for these patients was 16.7 kg, or 36.8 pounds, over one year on therapy.

LEPR Phase 3 Topline			
45.5% **p<0.0001**	**-12.5%** **p<0.0001**	**-41.9%** **p<0.0001**	**16.7kg or 36.8lbs**
>10% weight loss	**mean weight reduction**	**mean hunger score reduction**	**mean weight loss in 1 year**

In addition, the study design included a four-week placebo withdrawal period to further study the effect of treatment with setmelanotide. Upon entry into the placebo period, participants almost immediately gained weight and experienced an increase in hunger, reversing the downward trends in weight loss and hunger scores observed during the first 12 weeks of the treatment period. In both trials, the mean weight increase during the four-week placebo period was approximately 5 kg, or more than 11 pounds, and this weight gain was accompanied by a worsening in hunger scores. These trends reversed again when patients went back on drug.

We presented additional data from these trials showing the effect of setmelanotide on BMI scores and certain cardiovascular parameters in a special, late-breaking research forum during the 37th Annual Meeting of The Obesity Society at ObesityWeek® 2019, held November 3-7, 2019 in Las Vegas.

With this data, it was shown that setmelanotide was associated with reductions in BMI and BMI z-scores (BMI z-score, or BMI standard deviation scores, are measures of relative weight adjusted for child age and gender) for patients with POMC deficiency obesity who were treated with setmelanotide for over one year at therapeutic dose:

POMC deficiency obesity	**Baseline**	**~1 year at therapeutic dose**	**Percent change from baseline**
Participants aged ≥19 years, mean (SD) BMI, kg/m^2 (n=4)	43.90 (8.91)	34.58 (12.42)	-22.33 (14.75) *P*=0.056
Participants aged <19 years, mean (SD) BMI z-score (n=6)	3.35 (0.61)	1.73 (1.04)	-49.18 (27.20) *P*=0.007

Mean parameter (SD)[1]	**Diastolic blood pressure (mmHg)**[2]	**Systolic blood pressure (mmHg)**	**Heart rate (beats/min)**
Baseline	73.13 (10.75)	111.57 (7.78)	81.03 (12.08)
~1 year at therapeutic dose	71.50 (9.17)	109.83 (6.12)	75.37 (7.25)
Percent change from baseline, % *P* value	-1.81 (6.27) *P*=0.38	-1.36 (5.10) *P*=0.42	-5.85 (11.44) *P*=0.14

Setmelanotide was associated with reductions in BMI and BMI z-scores for patients with LEPR deficiency obesity who were treated with setmelanotide for over one year at therapeutic dose:

LEPR deficiency obesity	**Baseline**	**~1 year at therapeutic dose**	**Percent change from baseline**
Participants aged ≥19 years, mean (SD) BMI, kg/m^2 (n=8)	51.18 (10.67)	45.82 (11.48)[3]	-10.59 (8.11) *P*=0.01
Participants aged <19 years, mean (SD) BMI z-score (n=3)	3.52 (0.36)	3.03 (0.08)	-13.35 (8.87) *P*=0.12

Setmelanotide was not associated with significant changes in blood pressure or heart rate:

Mean parameter (SD)[4]	**Diastolic blood pressure (mmHg)**	**Systolic blood pressure (mmHg)**	**Heart rate (beats/min)**
Baseline	67.67 (5.83)	121.697 (8.84)	79.46 (12.60)
~1 year at therapeutic dose	66.48 (8.59)	115.111 (14.57)	77.89 (16.46)
Percent change from baseline, % *P* value	-1.58 (13.038) *P*=0.73	-3.78 (9.94) *P*=0.29	-1.32 (15.46) *P*=0. 80

1 N=10 for all POMC vital signs
[2] mmHG, millimeter of mercury
[3] N=7; one participant discontinued due to treatment-related adverse event.
[4] N=9 for all LEPR vital signs

Consistent with prior clinical experience, setmelanotide was generally well-tolerated in both of these pivotal trials. There were no reported cardiovascular adverse events, or AEs, related to setmelanotide. Setmelanotide was not associated with significant changes to blood pressure or heart rate. Treatment-emergent related AEs included injection site reactions, nausea and vomiting, and increased hyperpigmentation (darkening of the skin); these were consistent with prior clinical trials of setmelanotide. One LEPR study patient withdrew before the end of titration due to AE of mild hyper eosinophilia. One LEPR study patient died from injuries unrelated to the study drug. This patient was a passenger in a vehicle in a car accident and died from injuries from the accident.

We plan to complete and submit NDAs for POMC deficiency obesity and LEPR deficiency obesity in the first quarter of 2020.

Phase 3 trial in Bardet-Biedl and Alström syndromes

In December 2019, we announced that we had completed enrollment of the pivotal cohort in its Phase 3 clinical trial evaluating setmelanotide for the treatment of insatiable hunger and severe obesity in individuals living with BBS or Alström syndrome. We enrolled 32 individuals with BBS and six individuals with Alström syndrome in the pivotal cohort, and we are continuing to enroll patients in a supplemental cohort to meet demand and provide further data on the use of setmelanotide in people living with these conditions.

The combined pivotal Phase 3 trial is a multinational, open-label, single-arm study. Participants were randomized to placebo or setmelanotide for 14 weeks followed by an open-label period on setmelanotide for 52 weeks. The primary endpoint of the trial is the proportion of participants (≥12 years of age) who achieve at least 10% reduction in body weight from baseline at approximately 52 weeks of therapy. Key secondary endpoints include additional weight loss and hunger reduction analyses. Since the FDA agreed to include BBS and Alström syndrome under our Breakthrough Therapy designation, we received preliminary guidance on many aspects of the Phase 3 development programs in BBS and Alström syndrome. We believe that the combined trial, as opposed to two separate trials, is likely to lead to a more rapid path for approval of these two indications.

We expect to announce topline data from this pivotal cohort in the fourth quarter of 2020 or early in the first quarter of 2021.

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 in later sections below.

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

Setmelanotide: Key Clinical Programs in Monogenic MC4R 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	Topline data announced in 3Q2019	Topline data announced in 3Q2019	Initiated 2014, Completed 4Q2016 for these indications[5]	Initiated 2016[7][8]
Treatment groups[1]	Setmelanotide[2]	Setmelanotide[2]	Setmelanotide	Setmelanotide
Number of patients	10[3]	11[3]	2 POMC, 3 LEPR	Up to 150[9]
Patient demographics	Adult/pediatric POMC deficient[4]	Adult/pediatric LEPR deficient[4]	Adults/Adolescents	12 years of age or older[4] Multiple indications: POMC/PCSK1/LEPR heterozygous; POMC/PCSK1/LEPR compound heterozygous (two different mutations in gene) or homozygous deficiency obesity; POMC/PCSK1/LEPR composite heterozygous (two or more mutations in two or more genes) deficiency obesity; Smith-Magenis Syndrome (SMS); SH2B1 deficiency obesity; Chromosomal rearrangement of the 16p11.2 locus causing obesity; CPE compound heterozygous or homozygous deficiency obesity; Leptin deficiency obesity with loss of response to metreleptin; SRC1 deficiency obesity; MC4R 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; Spain; Netherlands; Canada; Greece; Israel

	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	Ongoing	Ongoing	Enrollment in pivotal cohort completed December 2019	Initiated 4Q2017
Treatment groups[1]	Setmelanotide[11]	No treatment[14]	Setmelanotide	No treatment[14]

Number of patients.....	Up to 150 patients[12]	Up to 1000 patients	32 BBS 6 Alström	10-20
Patient demographics.....	Any patient completing another setmelanotide clinical protocol[13]	Various[15]	Adult/Pediatric	Adult/pediatric[17] Patients with POMC, PCSK1 or LEPR deficiency obesity due to a bi-allelic loss of function genetic mutation
Duration of treatment.....	Multi-year Extensions	Open ended	52 weeks + Extensions	Up to 5 years
Location.....	Initiating in multiple countries	Initiating in multiple countries	United States including Puerto Rico, Canada, Spain, United Kingdom and France	Planned in Turkey, France and Sweden

(1) Setmelanotide, administered as once daily SC injection study.

(2) These trials include a placebo controlled, double-blind withdrawal period.

(3) 10 POMC deficiency obesity and 11 LEPR deficiency obesity patients were included in the pivotal cohort for each trial, but in agreement with the FDA, additional patients have been 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 ≥ 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 2019, 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 MC4R pathway disorders. In early 2018, both BBS and Alström provided proof of concept and moved to a phase 3 study. Our basket protocol continues to enroll patients with MC4R pathway disorders and is continuing to enroll and/or open sites.

(8) We have enrolled patients into the basket study who are diagnosed with POMC epigenetic disorders, as well as patients with POMC and other MC4R pathway gene mutations and anticipate additional indications for study possibly in 2019.

(9) We plan to study a larger number of patients with other MC4R 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 study treatment as defined 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 under their respective protocols, but such patients may also be eligible for one of our other interventional studies.

(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) Phase 3 protocol details for the combined BBS/Alström syndrome have been agreed with the FDA. The study includes a short randomized, placebo-controlled period for study validation. The Primary endpoint will be percent of subjects achieving 10% weight loss from baseline, the same as the endpoint for POMC deficiency obesity and LEPR deficiency obesity pivotal trials.

(17) Patients six years of age may be enrolled in our studies.

In addition, we have completed seven studies with setmelanotide in healthy obese subjects. These studies have evaluated safety, efficacy and pharmacokinetics after either a single- or multiple-doses of treatment. We have also completed a single study evaluating safety and pharmacokinetics with single- and multiple-doses of the long-acting, subcutaneous formulation of setmelanotide. Additionally, we have a single ongoing clinical study evaluating both the daily and long-acting formulations of setmelanotide, which plans to enroll approximately 48 healthy obese subjects (RM-493-026). Overall, approximately 450 subjects have been treated with setmelanotide.

Setmelanotide: Clinical Development Program in Genetically Defined Obesity

Phase 2 Clinical Development in POMC Deficiency Obesity

We 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 were treated with setmelanotide for more than two years, resulting in profound reductions of hyperphagia and body weight, with good tolerability. The first patient was a 20-year-old woman who, at three months of age, experienced the onset of obesity and hyperphagia. Ahead of the trial, the patient's self-reported trial hunger score, which is measured using a Likert score of zero to 10, where zero represents no hunger and 10 represents extreme hunger, was eight to nine out of 10 points, representing extreme hunger. She entered the trial with a baseline weight of 155 kg, or 341.7 lbs., and a BMI of 49.8 kg/m^2. The second patient was a 26-year old woman who also experienced early onset of obesity and hyperphagia. Ahead of the trial, the patient's self-reported trial hunger score was nine out of 10 points, representing extreme hunger. She entered the trial with a baseline weight or 152.8 kg, or 336.9 lbs. and a BMI of 54.1 kg/m^2.

The trial was an open label, ascending dose Phase 2 trial with a primary endpoint of weight loss and 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 treatment, the first patient demonstrated weight loss of 25.8 kg, or 56.9 lbs., representing 16.7% of her initial body weight. Hunger scores decreased from eight to nine prior to our trial to zero to one during the trial. During the subsequent three-week withdrawal period off drug, the patient regained 4.8 kg, or 10.6 lbs. and experienced a return to moderate to severe hunger. When setmelanotide treatment restarted after the withdrawal period, there was an immediate reduction of hunger and 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. After 42 weeks of treatment, the second patient demonstrated weight loss of 40.6 kg, or 89.5 lbs., representing 26.6% of her initial body weight. Hunger scores decreased from nine prior to the trial to one on most weeks during the trial. This patient continued on active treatment for 64 weeks and her weight stabilized at a weight loss of 40.5 kg, or 89.3 lbs. However, as a result of a misunderstanding regarding the dose of this patient's hydrocortisone treatment, her hunger score and weight briefly increased. 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. Setmelanotide was generally well tolerated in the POMC deficiency obesity Phase 2 trial, with few AEs, all mild and infrequent, and all previously reported in other clinical trials. The single serious adverse event was an influenza immunization reaction, which resulted in an overnight hospitalization and was considered unrelated to trial drug.

Phase 2 Clinical Development in LEPR Deficiency Obesity

We completed a Phase 2 proof of concept, open label clinical trial in three patients with LEPR deficiency obesity, in which these patients were treated with setmelanotide, resulting in reductions of hyperphagia and body weight, with good tolerability. The first patient was a 23-year old male who experienced early onset of obesity and hyperphagia. Ahead of the trial, this 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. The second patient was a 22-year old male who also experienced early onset of obesity and hyperphagia. Ahead of the trial, this 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. The third patient was a 14-year-old female adolescent, and the first adolescent patient treated with setmelanotide. Ahead of the 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.

After 61weeks of treatment, the first patient demonstrated total weight loss of 25.1 kg, or 55.3 lbs., representing 19.2% of his initial body weight. Hunger scores decreased from nine prior to the trial to one to two during this period. After 36 weeks of treatment, the second patient demonstrated weight loss of 13.9 kg, or 30.6 lbs., representing 11.4% of his initial body weight. Hunger scores decreased from 10 prior to the trial to 6 during this period. During a two-week period in which this patient independently discontinued treatment, he regained 5.2 kg, or 11.5 lbs., and his hunger scores increased to nine. Once treatment was re-initiated he experienced a significant reduction in hunger and a reduction in body weight. After 13 weeks of treatment, the third patient demonstrated weight loss of 10 kg, or 22 lbs., representing 8.3% of her initial body weight. Hunger scores decreased from nine prior to the trial to five during this period. However, this patient incorrectly performed the treatment injections, which we believe most likely precipitated an interval of weight regain during the trial period.

Phase 2 Clinical Development in Bardet-Biedl Syndrome

BBS 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 BBS is approximately 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. BBS 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 BBS. BBS 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 BBS 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 BBS. Studies in mouse models of BBS show that deficiencies in the MC4R pathway contribute to the obesity and hyperphagia in BBS, 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 BBS rodent models, where the mice respond to an MC4R agonist resulting in reduced food intake and body weight. The relation of BBS gene mutations to the MC4R pathway is supported by clinical data. Patients with BBS 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.

We are continuing to follow patients with BBS who are severely obese and enrolled in our phase 2 trial. We reported preliminary Phase 2 results for BBS in the fourth quarter of 2017 and updated the clinical status of these patients in 2018 and again in 2019. Results from the studies demonstrate that treatment with setmelanotide led to marked reductions in body weight and decreased appetite as shown by lower hunger scores. Safety data were consistent with previous clinical studies. In the second quarter of 2018, the FDA agreed to include BBS under our existing Breakthrough Therapy designation for setmelanotide.

For the Phase 2 trial, additional assessments of hunger using daily hunger scores and questionnaires were also obtained. We are using these assessments in our ongoing Phase 2 and Phase 3 trials and plan to continue using them in future trials. These 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 questions: “In the last 24 hours, on average, how hungry did you feel?” and “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 12 years of age and younger, we are obtaining a daily hunger score rating in response to the question “How hungry do you feel right now?” Patients are asked to give a response by choosing a pictorial of a smiley face and an associated hunger rating of 0 to 4, whereby 0 points signifies “not hungry at all” and 4 points indicates the patient feels his or her “hungriest possible.”

- 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, is used during site visits to count 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 24 points (8 questions with a maximum score of 3 points each), since this questionnaire tracks events and behavior not typically seen in patients with MC4R 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 BBS has been demonstrated by improvements in hunger and weight reduction, supporting that this is a setmelanotide-responsive, MC4R pathway disorder. The age of the patients ranged from 12 to 61 years. The starting weights of the patients ranged from 88.6 to 162.7 kg and BMI ranged from 37 to 51. 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 1, and 2 for a third adolescent patient.

Description of the Nine 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	24	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
6	16	5	122.4	43	Most hungry score = 8
7	14	4	88.6	37	Most hungry score = 7
8	13	*	171.76	51	FPD = 9 / SEQ = 2
9	31	1	162.7	48	Most hungry score = 6

*Genetic variant is not confirmed

Three patients with BBS type 1 mutations and one each with BBS types 2, 4, 5, 10, 12 mutations and one patient with a BBS mutation that was not established were enrolled. Total treatment durations up to 123 weeks. Six of the nine patients showed clinically important, marked weight loss. Hunger scores also were reduced in these six patients. Summary of the data is shown below and with six out of nine patients showing efficacy of > 10% weight loss supported moving into phase 3.

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

For six of the nine BBS patients who responded to treatment with setmelanotide, mean weight loss reached 22.1% of body weight, and mean hunger decreased by 53.8%. The time course of individual patient weight loss and hunger scores for these four patients who were treated for longer-term duration (108-123 weeks) are shown below, as updated and presented by us in September 2019.

Bardet-Biedl Patient Number	Treatment, weeks	Weight loss (kg)	Weight loss (lbs.)	Weight loss (%)	Decrease in hunger score (%)
1	123	54.2	119.5	36.7%	33.3%
2	119	14.7	32.4	14.8%	71.4%
3	121	33.9	74.7	27.9%	100.0%**
4	108	24.2	53.4	24.6%	66.7%
6	83	13.3	29.3	10.8%	37.5%
7	73	15.8	34.8	17.9%	14%***
Mean	**104.5**	**26.0kg**	**41.9 lbs.**	**22.1%**	**53.8%**

***Pt. has cognitive impairment, so Food Problem Diary (FPD) score maintained by caregiver; ***Pt. did not have baseline hunger measure. The first score was a 7, which was not recorded until after the patient had received treatment. Current score is a 6.*

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.

There were three patients who did not meet the responder definition by weight loss. Two of these patients withdrew from the study due to a lack of weight loss at 21 weeks and 36 weeks, respectively. One of these patients was clinically diagnosed with BBS, but this patient's BBS was not genetically confirmed. The third patient, who has 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%. Following treatment discontinuation, the patient gained 5.9 kg, appetite and hunger returned to baseline levels and HbA1c increased to 11.7%.

Overall setmelanotide was generally well tolerated in all patients in this BBS Phase 2 proof of concept study. Adverse events associated with setmelanotide treatment included increased pigmentation of the skin/nvi and mild injection site reactions. No discontinuations were due to adverse events. No serious adverse events were reported in BBS patients. No clinically significant detrimental changes in blood pressure or heart rate have been reported.

As stated above, we have completed enrollment of the pivotal cohort in December 2019 in a Phase 3 trial evaluating setmelanotide for the treatment of insatiable hunger and severe obesity in individuals living with BBS or Alström syndrome.

Phase 2 Proof of Concept Study of Patients with Alström Syndrome

Alström syndrome shares many clinical features with BBS, 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 BBS, recent scientific studies identify genetic deficiencies affecting the MC4R 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 MC4R pathway signaling. While Alström syndrome is less well studied than BBS, the similar pathophysiology of cilia dysfunction and clinical presentation support that deficiencies in the MC4R 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 from a phase 2 trial, 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 BBS. We the clinical status of these patients in September 2019. The FDA has also recently included Alström syndrome under our existing Breakthrough Therapy designation.

In December 2018, we initiated a phase 3 trial to evaluate the efficacy and safety of setmelanotide in patients with BBA and Alström syndrome, and we announced in December 2019 that we completed enrollment of the pivotal cohort.

As of September 2019, four Alström syndrome patients have been treated with setmelanotide in the Phase 2 study. The age of the patients ranges from 12 to 21 years. The starting weights of the patients range from 70.7 to 108.1 kg and BMI ranged from 28 to 47. The starting hunger scores for the adult patients ranged from 4 to 8 points on the 10-point scale.

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 27.9 kg/m^2 (above the 98^{th} percentile for his age). At baseline, his initial “worst hunger” score was 4 points, and his morning hunger score was 4 points. As of September 2019, this patient has been treated for 95 weeks including titration, most of the first 56 weeks’ time on a dose of 2 mg/day. During the course of 95 weeks of treatment, he experienced weight loss of 15.9 kg, or 35 lbs., which represented a 20.2% weight loss and a 25% decrease in hunger. Because his body weight was approaching ideal body weight, and he is a growing child, his dose was reduced to 1.5 mg/day, at 32 weeks and 0.5 mg six days/week at 50 weeks, with stabilization of his weight.

Three additional Alström patients (2 adolescents, 1 adult) have been enrolled in this Phase 2 study and the data is summarized below. One patient, the adult, did not show improvements in either weight or hunger and was discontinued. The third patient maintained weight and hunger score reduction while lowering HbA1c by 3% from 11% to 8%

Alström Syndrome Patient Number	Treatment Weeks	Weight loss (kg)	Weight loss (lbs.)	Weight loss (%)	Change in hunger score (Start/End)
1.....	95	15.9	35	20.2%	4/3
2.....	84	0.8	1.8	1.1%	8/5
3.....	68	5.4	11.9	5.9%	5/5

Overall, setmelanotide was generally well tolerated in all patients in this Alström syndrome Phase 2 proof of concept study. Adverse events associated with setmelanotide treatment included increased pigmentation of the skin/nevi and injection site reactions. No SAEs or discontinuations due to AEs were reported. No clinically significant increases in blood pressure were observed that resulted in the development of hypertension.

Our Phase 2 Basket Study: Phase 2 Proof of Concept Studies Focused on Patients with Monogenic Disorders of the MC4R Pathway

We are conducting Phase 2, proof of concept trials in a variety of monogenic, upstream disorders of the MC4R pathway, including, including POMC or LEPR heterozygous deficiency obesity, SRC1 deficiency obesity, SH2B1

deficiency obesity, MC4R deficiency obesity and Smith Magenis syndrome. Additionally, we are assessing setmelanotide in POMC epigenetic disorders and LEP and CPE deficiency obesities. 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 MC4R 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 are conducting these trials, as we did for the ongoing BBS 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.

We plan to enroll cohorts of approximately 10 patients each in these genetic populations. For the purposes of informing patient enrollment for genetically-identified cohorts (a-c, e, and g-j) DNA sequencing results for Basket-eligible genes are filtered and variants categorized based on our interpretation of the current state of scientific knowledge, both internal proprietary knowledge and published literature. DNA sequence data is filtered for rarity, defined as a population frequency of ≤1% in the publicly available GnomAD database (https://gnomad.broadinstitute.org/) and for nonsynonymous variants, defined by DNA changes resulting in alterations in amino acid sequence. Rare, nonsynonymous variants are then categorized based on current-state internal interpretation of the level of detrimental impact on the MC4R-pathway. DNA variants resulting in protein early termination, frameshifts, spicing errors or amino acid substitutions with confirmed biochemical loss-of-function are classified into a 'high-impact variant' categories due to the significant deleterious impact on protein, and subsequently, pathway function. Missense DNA variants lacking biochemical loss-of-function are classified into an 'other variant' category due to current uncertainty of the impact on protein and pathway function. Obese individuals carrying DNA variants in these categories, in genes eligible for the Basket protocol, are considered for enrollment and stratified into cohorts, accordingly. Depending upon the genotype and our computational or biological method for assessing loss-of-function, we may have several cohorts of "other variants."

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 POMC or LEPR Heterozygous Deficiency, or HET Obesity

POMC or LEPR heterozygous deficiency, or HET obesity is caused by the loss of one of the two genetic copies of POMC, PCSK1, or LEPR genes. Animal models support that such heterozygous deficiency in the MC4 receptor pathway can result in a predisposition to obesity. The effect of genetic heterozygous deficiency obesity was first demonstrated for another gene in the MC4R pathway: MC4R heterozygous deficiency obesity. Later data also supported that HET obesity results in a predisposition to obesity, though the epidemiology and clinical characterization of these patients is less well known. Our initial clinical focus is on patients with the most impactful variants, which we characterize as high-impact loss of function variants, to test the hypothesis that these 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 30kg/m^2, and who are carry a heterozygous variant of the POMC, LEPR, or PCSK1 gene. These patients have a genetic variant that may result in full or partial loss of POMC, PCKS1 or LEPR function. The purpose of studying these patients in this trial is to provide proof of concept that these patients will also demonstrate significant weight loss. We are enrolling this trial at sites in the United States and Europe, and reported initial results in June 2018 and updated those results in March 2019. With the latter data update, we announced plans to continue evaluating setmelanotide in POMC or LEPR heterozygous deficiency obesity, with patients enrolled into cohorts based on their loss-of-function (LOF) variants. This decision was based primarily on clinical results, which showed a more consistent treatment benefit in patients with higher-impact LOF variants.

In March 2019, we announced preliminary data from 13 patients with HET obesity who were treated with setmelanotide, including four patients with high-impact LOF variants and nine patients with other LOF variants:

- All four patients with high-impact LOF variants remained on therapy, including two patients who had been on treatment for more than 29 weeks, including any titration period, which can last 6-12 weeks before reaching a therapeutic dose. The first patient, who entered the study weighing 451 pounds, lost 40.5 pounds (9% body weight) and experienced a hunger score decrease of 90% after 37 weeks of treatment with setmelanotide. The second patient, who entered the study weighing 284 pounds, lost 49 pounds (17.3% body weight) and experienced a hunger score decrease of 71.4% after 29 weeks of treatment. The two additional patients had been on treatment for a short duration and showed promising weight loss and hunger score decreases during dose titration.

- Five of nine patients with other LOF variants remained on therapy, with treatment durations ranging from seven to 74 weeks. This includes the two responding patients on whom we reported data in June 2018. Across these five patients, one experienced a clinically meaningful weight loss of greater than 10%, three experienced weight loss between 5 and 8%, and one had been on treatment for a short duration and it was too early to assess response to therapy. Among the four response-evaluable patients, hunger score decreases ranged from 20 to 80%.

- Four of nine patients with other LOF variants discontinued treatment, including one patient who was discontinued due to lack of efficacy (previously reported in June 2018). The other three patients were discontinued following less than four weeks on therapy and therefore efficacy could not be evaluated. This includes the two patients on whom we reported in June 2018, both of whom discontinued due to AEs. In addition, one patient was withdrawn by the site for patient non-compliance.

POMC or LEPR heterozygous deficiency obesity is complex in many ways, in that there appears to be variable penetrance of obesity, in individuals with heterozygous mutations. As a result, we intend to study a larger number of 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.

b. SRC1 deficiency obesity

SRC1 is a transcriptional coactivator that has links to both the leptin receptor and to POMC. When the leptin receptor is activated, SRC1 through a cascade of events itself is activated and then goes on to drive the expression of POMC, such that in individuals who have heterozygote loss of function mutations in their SRC1 genes, there's insufficient leptin receptor activation of the MC4 receptor pathway, decreased POMC expression, which decreases the amount of available MSH to reactivate the MC4 receptor, consequentially resulting in that decreased activity that drives the hyperphagia and obesity in these individuals. The first academic paper describing SRC1 deficiency obesity, titled, “Steroid receptor coactivator-1 modulates the function of POMC neurons and energy homeostasis,” (Yang et al 2019, Nat Comm. 10, Article 1718) was published in *Nature Communications*. Based on our sequencing efforts, we estimate that there are more than 23,300 people in the United States living with SRC1 deficiency obesity.

c. SH2B1 deficiency obesity

SH2B1 is an adapter protein that amplifies the signal coming through the leptin receptor. In individuals who carry heterozygote loss of function mutations in SH2B1 or a chromosomal deletion that remove the SH2B1 from the chromosome, individuals have insufficient leptin receptor activity activation of their MC4 receptor pathway. This gives rise to a well-documented form of severe early-onset obesity and hyperphagia. Based on our sequencing efforts, we estimate that there are more than 24,000 people in the United States living with SH2B1 deficiency obesity.

d. MC4 receptor deficiency obesity

MC4R deficiency obesity may arise due to heterozygote loss of function mutations in the MC4 receptor gene itself, and this is one of the most well-known and most prevalent forms of monogenic severe early-onset 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.

An early Phase 1b study we conducted in downstream MC4R pathway defects demonstrated setmelanotide's potential efficacy and tolerability in upstream MC4R pathway deficiencies. 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.

Now with a very comprehensive ongoing biochemical screening study, we believe there is an opportunity for setmelanotide in a very defined subset of this broader population, specifically those individuals who carry MC4 receptor loss of function variants that can be overridden by setmelanotide. Based on our sequencing efforts, our addressable patient population estimate for MC4R deficiency obesity is greater than 10,000 patients in the United States.

e. Smith-Magenis syndrome

Smith-Magenis syndrome is a developmental disorder that affects many parts of the body. The major features of this condition include mild to moderate intellectual disability, delayed speech and language skills, distinctive facial features, sleep disturbances, behavioral problems, and in some cases, adolescent-onset obesity and hyperphagia. Smith-Magenis syndrome arises due to loss of function mutations or chromosomal deletions that effectively ablate the function of a gene called RAI1. RAI1 is a transcription factor that's been shown to affect the expression of a number of MC4 receptor pathway genes, including POMC itself. And as a result, we believe that in SMS, the hyperphagia and obesity is likely caused by an overall decrease in the activity of the MC4 receptor pathway.

Smith-Magenis syndrome affects at least 1 in 25,000 individuals worldwide. Many researchers believe that many people with this condition are not diagnosed, putting the prevalence closer to 1 in 15,000 individuals, according the National Institutes of Health. We estimate that approximately 2,400 individuals with Smith-Magenis syndrome have severe obesity and hyperphagia that may be addressable with setmelanotide.

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. Our academic collaborator in Berlin has an ongoing Phase 2 proof of concept trial to confirm the hypothesis that the subset of patients with very severe POMC epigenetic disorders may be highly responsive to setmelanotide therapy. There are currently no approved or effective therapies for these disorders.

Other MC4R Disorders

Based on setmelanotide's biochemical structure and mechanism of action, we believe setmelanotide has the potential to serve as replacement therapy for other rare genetic disorders of obesity which have pathophysiology upstream of the MC4R receptor. We are conducting research activities to study which potential disorders tied to the pathway may benefit from setmelanotide therapy. Our basket study protocols, which enable enrollment of new populations with disorders tied to the pathway, allow us to study new potential indications without the administrative and regulatory burden of initiating a separate clinical study de novo for each new indication.

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. We have expanded our genotyping study—the Genetic Obesity ID | Genotyping Study—in which eligible patients are genotyped for rare genetic disorders of obesity. As of the end of 2019, approximately 8,220 patients had been enrolled in our GO-ID study. The goal is to develop a screening algorithm for selecting patients to be genotyped and identified 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 approximately 100 genes which, in medical and scientific literature, have been associated with obesity, including other genes associated with the MC4R pathway. Individuals may enter the study through one of three arms including: a history of severe, early onset obesity, and hyperphagia, high BMI, and individuals within three months of bariatric surgery. The study is currently enrolling in the United States and Europe and is expected to expand to a total of 140 sites worldwide. 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.

Uncovering Rare Obesity

In July 2019, we announced the launch of Uncovering Rare Obesity, a free genetic testing program that may help determine if individuals have an underlying genetic cause of their severe obesity. As severe obesity is epidemic in the United States, we are focused on identifying people with early-onset obesity that may be caused by certain rare genetic variants. As part of these efforts, we have launched Uncovering Rare Obesity in order to increase access to genetic testing. As of December 31, 2019, 1,120 United States health care providers have requested 5,738 Uncovering Rare Obesity kits, and 1,580 sequencing tests have been ordered and patient samples collected.

This program complements several initiatives designed to advance the understanding of genetic causes of severe obesity, and Uncovering Rare Obesity broadens these efforts and brings access to genetic testing into the community setting. Currently available physician-ordered genetic testing panels are often cost prohibitive, while many consumer genetic tests are incomplete when it comes to genetic disorders of obesity. This makes it difficult to confirm an underlying genetic cause of severe obesity. We believe the program marks an important step in the understanding of these disorders that might help patients and their families find new diagnosis and treatment strategies in the years ahead.

We are partnering with PreventionGenetics, a Clinical Laboratory Improvement Amendments (CLIA)-certified independent laboratory, to conduct the genetic testing for Uncovering Rare Obesity. This program covers the cost of the test and excludes office visit, copay, sample collection, and any other related costs to a participant. In addition, as part of the program, licensed genetic counselors from PWN Health, a leading provider of professional guidance for diagnostic and genetic testing, are available to advise participating individuals.

Long-Acting Setmelanotide Pharmacokinetic Trial

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.

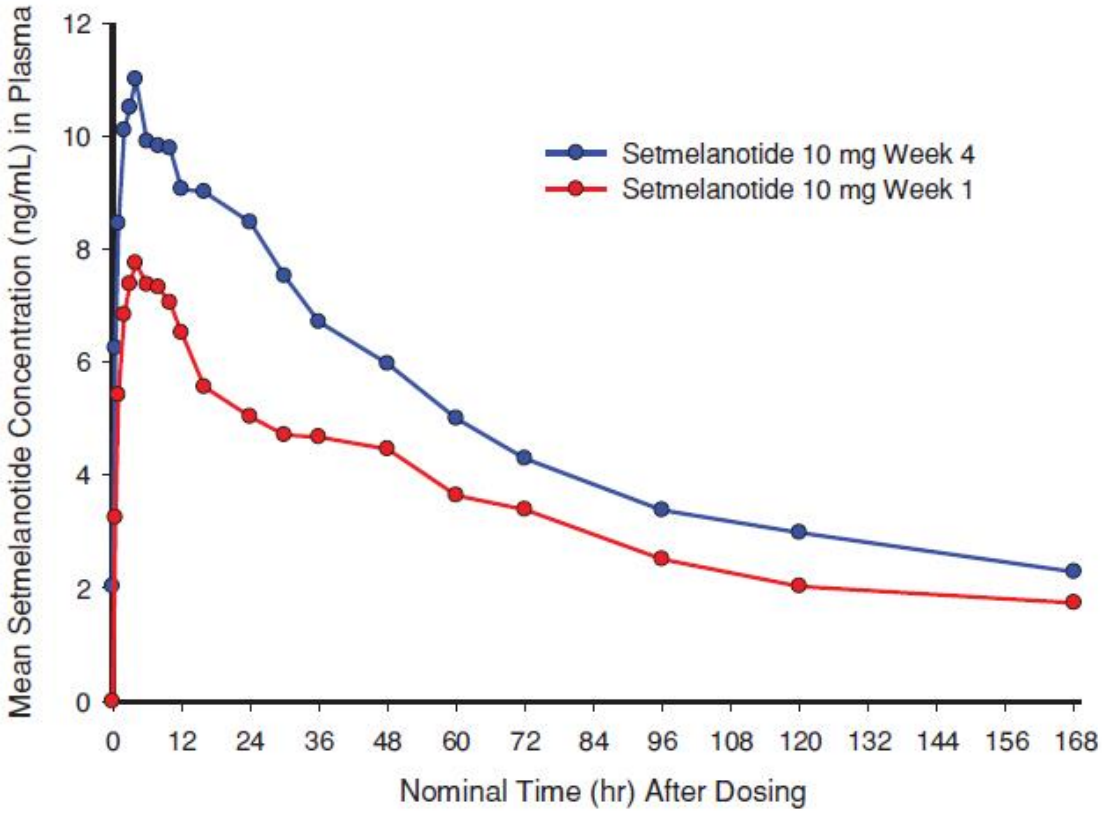
We have compelling preclinical data with the long-acting formulation: in monkeys, the terminal half-life of the long-acting formulation is approximately 105 hours, and in rats, approximately 92 hours. Two-week toxicology studies in rats have been completed, and the long-acting formulation was well tolerated. 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 complete, 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, this simpler dosing regimen may provide improvements in patient convenience and may provide additional advantages in the pediatric population.

We also completed a single study evaluating safety and pharmacokinetics with single- and multiple-doses of the long-acting, subcutaneous formulation of setmelanotide, and we have a single ongoing clinical study evaluating both the daily and long-acting formulations of setmelanotide. We anticipate completing these studies in 2020, and upon analysis of the data, we will seek dialogue with the FDA to develop a regulatory strategy for this once-weekly formulation of setmelanotide.

Mean setmelanotide concentrations (ng/mL) in plasma during weeks 1 and 4 following 10 mg subcutaneous weekly injections of a Camurus formulation



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	22 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	99 healthy obese subjects	Completed
RM 493 018 ..... A Long-Acting Formulation PK Study of RM-493	Obesity	SC injection of long-acting formulation	42 healthy obese subjects	Parts A and B completed

SC=subcutaneous.

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.

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, 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. Monitoring for blood pressure and heart rate changes, as well as other potential AEs, is included in all setmelanotide clinical trials.

Because of these first generation MC4R 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, Phase 2 and Phase 3 clinical trials. Overall, except as outlined below, the number and patterns of AEs was generally low, and the intensity of the AEs was generally mild, and infrequently led to clinical trial discontinuation.

There has been only a single SAE 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.

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 MC4R therapies. While the preliminary data are encouraging, there will be continued focus on potential cardiovascular risk until addressed in larger and longer clinical trials.

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.

Overall, the most common AEs reported among setmelanotide treated patients have been skin hyperpigmentation, injection site reactions, nausea, headache, vomiting, decreased appetite, and diarrhea.

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 MC4R 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 first of which, in mice is ongoing, and with 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. The EMA has agreed that only the mouse study will be required around the time of any setmelanotide approval.

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 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.

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 MC4R 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.

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 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 MC4R 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), Saniona, Zafgen (ZGN-1258), GLWL Research Inc. (GLWL-01), Insys Therapeutics Inc. (Oral Cannabidiol Solution) and Calm Therapeutics.

Licensing Agreements

Ipsen Pharma S.A.S.

Pursuant to a license agreement with Ipsen Pharma S.A.S., or Ipsen, we have 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 MC4R 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, we have 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.

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 MC4R 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 collaborations 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. Our goal is for our field personnel to work directly with patients, caregivers and healthcare providers to facilitate therapy initiation and adherence. 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. 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 organization in the United States and core strategic markets and to selectively establish collaborations 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 MC4R 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 December 31, 2019, 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 have filed eight United States patent applications and 43 non-United States applications in 12 jurisdictions.

In the patent family directed to selected MC4R 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, subject to fulfillment of specific criteria, 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 various third parties for the manufacture of setmelanotide and intend to continue to do so in the future. We have entered into process development and manufacturing service agreements with three CMOs: Corden Pharma Brussels S.A, or Corden, formerly Peptisyntha SA prior to its acquisition by Corden, PolyPeptide Group, Baine L'Alleud, or PPL, and Neuland Laboratories, in connection with certain process development and manufacturing services for regulatory starting materials and/or drug substance, or API, 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 has agreed to provide certain process development and manufacturing services in connection with the manufacture of setmelanotide drug product. Under our agreements, we pay these third parties for services in accordance with the terms of mutually agreed upon work orders, which we may enter into from time to time. We also may terminate the agreement or any work order thereunder upon at least 60 days' prior written notice to Recipharm. 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. Under the current agreements, each party is subject to customary indemnification provisions.

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, including pharmacovigilance, 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. In December 2019, Congress eliminated the statutory “chemically synthesized polypeptide” exclusion. Nevertheless, because of FDA’s statements with regard to the scope of the products that will be affected by this change, and the size of our products (fewer than 40 amino acids), 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.

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.

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.

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 AEs 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. The FDA's regulations governing the acceptance of foreign clinical studies not conducted under an IND or an NDA require that such studies 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 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 SAEs 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 is typically iterative. 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, BBS, 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.

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 AEs, 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 nine 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 FDA'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 AEs 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. The Creating and Restoring Equal Access To Equivalent Samples Act (the CREATES Act), which was enacted by Congress in December 2019, created new causes of action against innovator companies that refuse to provide samples of drugs for purposes of developing generic products or that refuse to allow generic companies to participate in a shared REMS.

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.

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. 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 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 within 60 days of the date 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. The FDA recently reiterated its position that a Laboratory Developed Test, or LDT, is sufficient for identifying patients in our clinical trials for setmelanotide, but the agency also recently indicated that an *in vitro* companion diagnostic device, or companion diagnostic,will be needed. The FDA stated that absence of complete development of a companion diagnostic would not preclude us from submitting an NDA or preclude the FDA from reviewing it. The FDA also stated that completing development of a companion diagnostic as a post-marketing commitment or a post-marketing requirement is a possibility, assuming that upon review, no issues related to efficacy or safety arise that would necessitate a companion diagnostic at the time of approval. The FDA committed to working with us to identify the least burdensome analytical validation approach to a companion diagnostic for setmelanotide. We are engaged in ongoing discussions with FDA regarding the development of a Class II companion diagnostic.

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 stated that it generally requires *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. In recent correspondence, however, FDA has stated that a companion diagnostic for setmelanotide is a good candidate for a de novo application.

A de novo application is a mechanism that permits a low or moderate risk classification for new devices that otherwise would be classified into the highest risk category, Class III. Specifically, devices of a new type that the FDA has not previously classified based on risk previously were automatically classified into Class III by operation of the FDC Act, regardless of the level of risk they posed. To avoid requiring PMA review of low- to moderate-risk devices classified in Class III by operation of law, Congress enacted a provision to allow FDA to classify a low- to moderate-risk device not previously classified into Class I or II. To grant a request for de novo classification, FDA must find that general controls or general and special controls provide a reasonable assurance of safety and effectiveness for the device.

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.

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, pharmacovigilance, promotion, advertising 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 conduct 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 Clinical Trials Regulation introduces a complete overhaul of the existing legislation governing clinical trials for medicinal products in the EU. This includes a new coordinated procedure for authorization of clinical trials that is reminiscent of the mutual recognition procedure for marketing authorization of medicinal products, and increased obligations on sponsors to publish clinical trial results. 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 European Medicines Agency, or 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. By a decision of 15 June 2018, the EMA formally accepted the PIPs for setmelanotide in the treatment of appetite and general nutritional disorders. This included the deferral and 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. Medicinal products that contain a new active substance that is not yet authorized in the EEA and medicinal products that constitute a significant therapeutic, scientific or technical innovation or for which a centralized process is in the interest of patients within the EU fall within the optional scope of the centralized marketing authorization procedure.

Under the centralized procedure, 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 by the CHMP 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 EMA's 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 product developers to participate in a voluntary scheme of enhanced interaction and early dialogue with the EMA, 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 submission of a separate application to, and leads to grant of separate marketing authorizations 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 assessment of the application for marketing authorization is conducted by the reference EU member state. This 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 Heads of Medicines Agencies, or CMDh for review. This review, which may also be escalated to the CHMP in case of disagreement in CMDh would result in a decision by the European Commission, whose decision is binding on all EU member states.

The mutual recognition procedure permits companies that have a medicinal product already authorized in one EU member state to apply for this authorization to be recognized by the competent authorities in other EU member states. The national marketing authorization procedure is founded on the same basic EU regulatory process as the other marketing authorization procedures discussed in this Section. The national marketing authorization procedure, which is increasingly rare, permits a company to submit an application to the competent authority of a single EU member state and, if successful, to obtain a marketing authorization that is valid only in this EU member state.

Regulatory Data Protection in the European Union

In the European Union, innovative medicinal products authorized 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 or biosimilars of these innovative products from referencing the innovator's data to assess a generic (abbreviated) or biosimilar application for a period of eight years. During an additional two-year period of market exclusivity, an application for the marketing authorization of a generic or biosimilar medicinal product can be submitted and a related marketing authorization may be granted, and the innovator's data may be referenced, but no generic or biosimilar 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 medicinal product is granted data and market 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 EU

member states 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 advertising and promotion of medicinal 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.

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 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.

In April 2017, the EU Regulation on In Vitro Diagnostic Medical Devices (Regulation (EU) 2017/746), or IVDR, was adopted. The IVDR repeals and replaces Directive 98/79/EC. Unlike directives, which must be implemented into the national laws of the individual EU member states, the IVDR will be directly applicable in the EU member states and on the basis of the EEA agreement in Iceland, Liechtenstein and Norway. The IVDR is, among other things, intended to establish a uniform, transparent, predictable and sustainable regulatory framework across the EEA for *in vitro* diagnostic medical devices and ensure a high level of safety and health while supporting innovation. The IVDR will apply beginning on 26 May 2022. Once applicable, the IVDR will introduce new classification rules for *in vitro* diagnostic medical devices and new regulatory requirements. The IVDR will also impose increased compliance obligations for manufacturers of *in vitro* diagnostic medical devices to access the EEA market. Moreover, the scrutiny imposed by notified bodies for the technical documentation related these devices will increase considerably.

Brexit and the Regulatory Framework in the United Kingdom

Following a national referendum and enactment of legislation by the government of the United Kingdom, the United Kingdom formally withdrew from the EU on January 31, 2020 and entered into a transition period during which it will continue its ongoing and complex negotiations with the EU relating to the future trading relationship between the parties. Significant political and economic uncertainty remains about whether the terms of the relationship will differ materially from the terms before withdrawal, as well as about the possibility that a so-called “no deal” separation will occur if negotiations are not completed by the end of the transition period.

Further, the United Kingdom’s withdrawal from the EU has resulted in the relocation of the EMA from the United Kingdom to the Netherlands. This relocation has caused, and may continue to cause, disruption in the administrative and medical scientific links between the EMA and the U.K. Medicines and Healthcare products Regulatory Agency, including delays in granting clinical trial authorization or marketing authorization, disruption of importation and exportation of active substance and other components of new drug formulations, and disruption of the supply chain for clinical trial product and final authorized formulations. The cumulative effects of the disruption to the regulatory framework may add considerably to the development lead time to marketing authorization and commercialization of products in the EU and/or 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. The downward pressure on healthcare costs in general, and particularly in relation to prescription only medicinal products, has become more intense. As a result, increasingly high barriers are being erected to the entry of new products.

Health Technology Assessment, or HTA, of medicinal products is, however, 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.

As a further step in this direction, on January 31, 2018, the European Commission adopted a proposal for a regulation on HTA. This legislative proposal is intended to boost cooperation among EU member states in assessing health technologies, including new medicinal products, and providing the basis for cooperation at the EU level for joint clinical assessments in these areas. The proposal would permit EU member states to use common HTA tools, methodologies, and

procedures across the EU, working together in four main areas, including joint clinical assessment of the innovative health technologies with the most potential impact for patients, joint scientific consultations whereby developers can seek advice from HTA authorities, identification of emerging health technologies to identify promising technologies early, and continuing voluntary cooperation in other areas. Individual EU member states will continue to be responsible for assessing non-clinical (e.g., economic, social, ethical) aspects of health technology, and making decisions on pricing and reimbursement. The European Commission has stated that the role of the draft HTA regulation is not to influence pricing and reimbursement decisions in the individual EU member states. However, this consequence cannot be excluded.

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 healthcare Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, or receiving remuneration (anything of value), 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 exceptions and regulatory safe harbors to the federal Anti-Kickback Statute protecting certain common business arrangements and activities from prosecution or regulatory sanctions, the exceptions 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 exception 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. Such private individuals may share in amounts paid by the entity to the government in recovery or settlement. 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. False Claims Act liability is potentially

significant in the healthcare industry because the statute provides for treble damages and significant mandatory penalties per false or fraudulent claim or statement for violations. Because of the potential for large monetary exposure, healthcare and pharmaceutical companies often resolve allegations without admissions of liability for significant and material amounts to avoid the uncertainty of treble damages and per claim penalties that may be awarded in litigation proceedings. Settlements may require companies to enter into corporate integrity agreements with the government, which may impose substantial costs on companies to ensure compliance. 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, including private third-party payors, 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. Similar to the federal healthcare Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it to have committed a violation;

- HIPAA and its implementing regulations, which impose obligations with respect to safeguarding the privacy, security and transmission of individually identifiable health information. We may obtain health information from third parties (including research institutions from which we obtain clinical trial data) that are subject to privacy and security requirements under HIPAA. Although we are not directly subject to HIPAA – other than with respect to providing certain employee benefits – we could potentially be subject to criminal penalties if we, our affiliates, or our agents knowingly obtain, use, or disclose individually identifiable health information maintained by a HIPAA-covered entity in a manner that is not authorized or permitted by HIPAA;

- the federal Physician Payments Sunshine Act, implemented as the Open Payments Program requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report annually to the United States Department of Health and Human Services, Centers for Medicare and Medicaid Services, information related to payments and other transfers of value to physicians (defined to include doctors, dentists, optometrists, podiatrists, and chiropractors) and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members.Beginning in 2022, applicable manufacturers also will be required to report information regarding payments and transfers of value provided to physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, and certified nurse-midwives. Manufacturers must submit reports 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 items or services that are reimbursed under Medicaid and other state programs or, in several states, by non-governmental third-party payors, including private insurers.

In addition to the foregoing requirements, 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.

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act of 2010, or collectively the ACA, made significant changes to the Medicaid Drug Rebate Program. The ACA is discussed in greater detail under the heading "Healthcare Reform" and under the risk factor "*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 this Annual Report on Form 10-K.

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, which is administered by the Health Resources and Services Administration, or HRSA, 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.

HRSA issued a final regulation regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities, which became effective on January 1, 2019. It is currently unclear how HRSA will apply its enforcement authority under the new regulation. HRSA also has implemented a reporting requirement pursuant to which participating manufacturers are required to report the 340B ceiling prices for their drugs to HRSA every quarter. 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 and Medicare Part B programs 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).

The FCP is based on the Non-Federal Average Manufacturer Price, or Non-FAMP, which we would be required to calculate and report to the VA on a quarterly and annual basis. Pursuant to applicable law, knowing provision of false information in connection with a Non-FAMP filing can subject a manufacturer to significant civil monetary penalties for each item of false information. The FSS pricing and contracting obligations also contain extensive disclosure and certification requirements.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 this Annual Report on Form 10-K.

Additionally, 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, several states require pharmaceutical companies to implement compliance programs and/or marketing codes. 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 and/or genetic 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, constantly evolving, 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. Various state and federal regulatory and enforcement agencies continue actively to investigate violations of health care laws and regulations, and the United States Congress and state legislatures continue to strengthen the arsenal of enforcement tools. Enforcement agencies also continue to pursue novel theories of liability under these laws. In particular, government agencies recently have increased regulatory scrutiny and enforcement activity with respect to manufacturer reimbursement support activities and patient support programs, including bringing criminal charges or civil enforcement actions under the federal health care Anti-Kickback statute, civil False Claims Act and violations of health care fraud and HIPAA privacy provisions. 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.

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.

In California, the California Consumer Privacy Act (“CCPA”) took effect on January 1, 2020. The CCPA establishes certain requirements for data use and sharing transparency and creates new data privacy rights for consumers. These laws and regulations are evolving and subject to interpretation, and may impose limitations on our activities or otherwise adversely affect our business. Similarly, there are a number of legislative proposals in the European Union, the United States, at both the federal and state level, as well as other jurisdictions that could impose new obligations or limitations in areas affecting our business. In addition, some countries are considering or have passed legislation implementing data protection requirements or requiring local storage and processing of data or similar requirements that could increase the cost and complexity of delivering our services and research activities. These laws and regulations, as well as any associated claims, inquiries or investigations or any other government actions may lead to unfavorable outcomes including increased compliance costs, delays or impediments in the development of new products, negative publicity, increased operating costs, diversion of management time and attention, and remedies that harm our business, including fines or demands or orders that we modify or cease existing business practices.

In the EU, interactions between pharmaceutical companies and physicians are also governed by strict laws, regulations, industry self-regulation codes of conduct and physicians’ codes of professional conduct in the individual EU member states. The provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products is prohibited in the EU. The provision of benefits or advantages to physicians is also governed by the national anti-bribery laws of the EU member states. One example is the UK Bribery Act 2010. This Act applies to any company incorporated in or “carrying on business” in the UK, irrespective of where in the world the alleged bribery activity occurs. This Act could have implications for our interactions with physicians in and outside the UK. Violation of these laws could result in substantial fines and imprisonment.

Payments made to physicians in certain EU member states must be publically disclosed. Moreover, agreements with physicians must often be the subject of prior notification and approval by the physician’s employer, their competent

professional organization, and/or the competent authorities of the individual EU member states. These requirements are provided in the national laws, industry codes, or professional codes of conduct, applicable in the individual EU member states. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

Failure to comply with the EU member state laws implementing the Community Code on medicinal products, and EU rules governing the promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices, with the EU member state laws that apply to the promotion of medicinal products, statutory health insurance, bribery and anti-corruption or with other applicable regulatory requirements can result in enforcement action by the EU member state authorities, which may include any of the following: fines, imprisonment, orders forfeiting products or prohibiting or suspending their supply to the market, or requiring the manufacturer to issue public warnings, or to conduct a product recall.

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 AE 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 may, therefore, rely only 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, the 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 EU 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.

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 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 Medicaid managed care 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;

- expansion of the list of entity types eligible for participation in the Public Health Service 340B drug pricing program, or the 340B program, to include certain free-standing cancer hospitals, critical access hospitals, rural referral centers, and sole community hospitals, but exempting "orphan drugs" from the 340B ceiling price requirements for these covered entities;

- 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; 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 2029.

Certain provisions of the ACA have been subject to judicial challenges as well as efforts to repeal or replace them or to alter their interpretation or implementation. 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," effective January 1, 2019. Further, the Bipartisan Budget Act of 2018 among other things, amended the Medicare statute, effective January 1, 2019, to reduce the coverage gap in most Medicare drug plans, commonly known as the "donut hole," by raising the manufacturer discount under the Medicare Part D coverage gap discount program to 70%. Additional legislative changes, regulatory changes, and judicial challenges related to the ACA remain possible, but the nature and extent of such potential additional changes are uncertain at this time. It is unclear how the ACA and its implementation, as well as efforts to repeal or replace, or invalidate, the ACA, or portions thereof, will affect our business.It is possible 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

As of December 31, 2019, we had 70 full-time employees.

Corporate Information

We are a Delaware corporation organized in February 2013. Our principal executive offices are located at 222 Berkeley Street, 12th Floor, Boston, MA 02116, and our telephone number is (857) 264-4280. Our website is www.rhythmtx.com. Information that is contained on, or that can be accessed through, our website is not incorporated by reference into this Annual Report on Form 10-K, and you should not consider information on our website to be part of this Annual Report on Form 10-K.

Available Information

We make available free of charge on the investor relations portion of our website our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, Proxy Statements for our annual meetings of stockholders, and amendments to those reports, as soon as reasonably practicable after we file such material with, or furnish it to, the Securities and Exchange Commission, or SEC. These filings are available for download free of charge on the investor relations portion of our website located at https://ir.rhythmtx.com. The SEC also maintains a website that contains reports, proxy statements and other information about issuers, like us, that file electronically with the SEC. The address of that website is https://www.sec.gov.

Item 1A. Risk Factors

Our operations and financial results are subject to various risks and uncertainties, including those described below, which could adversely affect our business, financial condition, results of operations, cash flows, and the trading price of our common stock. Additional risks and uncertainties that we currently do not know about or that we currently believe to be immaterial may also impair our business. You should carefully consider the risks described below and the other information in this Annual Report on Form 10-K, including our audited consolidated financial statements and the related notes thereto and "Management's Discussion and Analysis of Financial Condition and Results of Operations."

Risks Related to Our Financial Position and Need for Capital

We are a late-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 late-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. 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 four indications, POMC deficiency obesity, LEPR deficiency obesity, Bardet-Biedl syndrome, or BBS, and Alström syndrome and in Phase 2 clinical development for other indications. We have funded our operations to date primarily through the proceeds from the sales of common stock and preferred stock as well as capital contributions and have incurred losses in each year since our inception.

Our net losses were $140.7 million, $74.1 million and $33.7 million for the years ended December 31, 2019, 2018 and 2017, respectively. As of December 31, 2019, we had an accumulated deficit of $325.3 million. Substantially all of our operating losses have resulted from costs incurred in connection with our development programs and from commercial and 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 incur 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:

- continue to initiate and successfully complete later-stage clinical trials that meet their clinical endpoints;
- continue to 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 MC4R pathway;

- successfully manufacture or contract with others to manufacture setmelanotide;
- ensure setmelanotide is available to patients with rare genetic disorders of obesity;
- 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 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.

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 our available cash resources 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.

From August 2015 through August 2017, we raised aggregate gross proceeds of $81.0 million through our issuance of series A preferred stock. Since our initial public offering, or IPO, through our October 18, 2019 public offering, we have raised aggregate gross proceeds of our common stock of approximately $484.5 million before deducting underwriting discounts, commissions and estimated offering related transaction costs. As of December 31, 2019, our cash and cash equivalents and short-term investments were approximately $292.5 million. We expect our existing cash and cash equivalents and short-term investments will enable us to fund our operating expenses through at least the end of 2021. 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 were incorporated in February 2013 and 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 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 relatively new business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. We will need to begin transitioning 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 may not be a reliable indicator of our future results.

The historical financial information we have included in this Annual Report on Form 10-K may not reflect our future results of operations, financial position and cash flows because our historical financial information does not reflect changes that we have incurred and expect to continue to incur as we transition to a commercial company including changes in cost structure, personnel needs, financing and operations of our business. In addition, our financial results may vary from quarter to quarter and from year to year in response to a variety of factors beyond our control. As a result, it may be difficult for investors to compare our future results to historical results or to evaluate our relative performance or trends in our business.

Risks Related to the Development of Setmelanotide

The reported results of our Phase 3 clinical trials for POMC and LEPR deficiency obesities are based on topline data and may ultimately differ from actual results once additional data are received and fully evaluated.

The reported results of our Phase 3 clinical trials for POMC and LEPR deficiency obesities that we have publicly disclosed consist of topline data. Topline data are based on a preliminary analysis of currently available efficacy and safety data, and therefore the reported results, findings and conclusions related to such trial are subject to change following a comprehensive review of the more extensive data that we expect to receive related to such trial. Topline data are based on important assumptions, estimations, calculations and information currently available to us, and we have not received or had an opportunity to fully and carefully evaluate all of the data related to the trial. As a result, the topline results of our Phase 3 trials that we have reported may differ from future results, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. In addition, third parties, including regulatory agencies, may not accept or agree with our assumptions, estimations, calculations or analyses or may interpret or weigh the importance of data differently, which could impact the potential for approval of setmelanotide, or if approved, the labeling and commercial value of setmelanotide and our business in general. If the topline data that we have reported

related to our Phase 3 trials differ from actual results, our ability to obtain approval for, and commercialize, our products may be harmed, which could harm our business, financial condition, operating results or prospects.

The FDA and EMA may disagree with our interpretation of clinical results obtained from our Phase 3 clinical trial for POMC and LEPR deficiency obesities, our results do not guarantee that the NDA we submit will be accepted for review or will support regulatory approval, and, even if our Phase 3 data are deemed to be positive by the FDA or EMA, the FDA or EMA may disagree with other aspects of the NDA and, as a result, the FDA or the European Commission may decline to approve setmelanotide for the proposed indications.

We have reported positive topline data from our Phase 3 clinical trials for POMC and LEPR deficiency obesities. However, even if we believe that the data from the trial are positive, the FDA or EMA could determine that the data from such trial were negative or inconclusive, not sufficiently meaningful from a clinical perspective or could reach different conclusions than we have on the same data. Negative or inconclusive results of a clinical trial or a difference of opinion could cause the FDA or the European Commission to decline to approve our application or cause the FDA or EMA to require us to repeat the trial or conduct additional clinical trials prior to obtaining approval for commercialization, and there is no guarantee that additional trials would achieve positive results to the satisfaction of the FDA or EMA or that the FDA or EMA will agree with our interpretation of the results. Any such determination by the FDA or EMA would delay the timing of our commercialization plan for setmelanotide or prevent its further development, and adversely affect our business operations. Additionally, the FDA or EMA may not accept our NDA for review and may provide commentary at any time during the review process which could require us to submit additional information and delay the review timeline, adversely affect the review process, or even prevent the approval of setmelanotide, any of which would adversely affect our business. We may not be able to appropriately remedy issues that the FDA or EMA may raise in its review of our NDA submission or equivalent EU submission, and we may not have sufficient time or financial resources to conduct future activities to remediate issues raised by the FDA or EMA.

There is no guarantee that the data obtained from our Phase 3 clinical trials for POMC and LEPR deficiency obesities will be supportive of, or guarantee, a successful NDA submission, or result in our obtaining FDA or the European Commission's approval of setmelanotide in a timely fashion and for a commercially viable indication, or at all. For example, the FDA or EMA could determine that the trial did not meet its objectives or the FDA or EMA could still have concerns regarding the conduct of the Phase 3 trials. At any future point in time, the FDA or EMA could require us to complete further clinical or preclinical trials, or take other actions which could delay or preclude any NDA submission or approval of the NDA or equivalent EU approval and could require us to obtain significant additional funding. There is no guarantee such funding would be available to us on favorable terms, if at all, nor is there any guarantee that FDA or EMA would consider any additional information complete or sufficient to support approval. If an NDA for setmelanotide is submitted, the FDA may hold an advisory committee meeting to obtain committee input on the safety and efficacy of setmelanotide. Typically, advisory committees will provide responses to specific questions asked by the FDA, including the committee's view on the approvability of the product candidate under review. Advisory committee decisions are not binding but an adverse decision at the advisory committee may have a negative impact on the regulatory review of setmelanotide. Additionally, we may choose to engage in the dispute resolution process with the FDA if we do not receive approval, which could extend the timeline for any potential approval.

There is no assurance that our NDA or similar submission with the EMA will be submitted within the timeframes we expect. Further, if we are able to submit an NDA or equivalent EU submission for setmelanotide with the clinical data from our Phase 3 trials, there is no guarantee that such data will be deemed sufficient by the FDA or EMA. There is no guarantee that the FDA or EMA will deem our trial protocols or results from the study sufficient when they are formally reviewed as a part of an NDA or EU equivalent submission even though we discussed the design of the trials with FDA and EMA prior to commencing the trials. The FDA and EMA each have significant discretion in the review process, and we cannot predict whether the FDA or EMA will agree with our conclusions regarding the results of the Phase 3 trials, including whether our data are reliable and generalizable.

Moreover, even if we obtain approval of setmelanotide, any such approval might significantly limit the approved indications for use, including by limiting the approved label for use by more limited patient populations than we propose, require that precautions, contraindications or warnings be included on the product labeling, including black box warnings, require expensive and time-consuming post-approval clinical studies, risk evaluation and mitigation strategies, or REMS,

or surveillance as conditions of approval, or, through the product label, the approval may limit the claims that we may make, which may impede the successful commercialization 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, or initial results from our Phase 3 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 and Phase 3 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, BBS and Alström syndrome, four genetic disorders of extreme and unrelenting appetite and obesity, in which setmelanotide dramatically reduced both weight and hunger. We have also reported positive topline results from our pivotal Phase 3 clinical trials in POMC deficiency obesity and LEPR deficiency obesity, which demonstrated a clinically meaningful impact on reductions of weight and hunger. We hypothesize that patients with other upstream genetic defects in the MC4R 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.

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 FDA will require for our first approval, and which we believe outlines the studies the 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 an NDA for setmelanotide. While we may submit carcinogenicity study results in the NDA submission to support regulatory approval, we may decide to defer the submission of all carcinogenicity studies until after we receive regulatory approval to market setmelanotide in the United States.

In June 2018, setmelanotide was designated as PRIority MEdicine, or PRIME, by the EMA's Committee for Medicinal Products for Human Use, or CHMP. Acknowledging that setmelanotide targets an unmet medical need, the EMA offers enhanced support in the development of the medicinal product through enhanced interaction and early dialogue to optimize our development plans and speed up regulatory evaluation in the EU. As part of this designation, the EMA has provided guidance to us concerning the development of setmelanotide. The EMA advised us that we should include the mouse carcinogenicity study in our initial filing for marketing authorization in the EU. We cannot be certain

how long it will take to complete the mouse carcinogenicity study required to be included in our application for marketing authorization, and this could delay the timing of submission of a potential marketing authorization in the EU. The EMA also advised us that it will not require the rat carcinogenicity study until post approval. However, the EMA does not provide as firm guidance as the FDA, and accordingly, there can be no guarantee that we will be able to achieve this deferral of the rat carcinogenicity study, which could impact the timing of grant of any potential marketing authorization in the EU.

In addition, 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 have indicated whether they agree with our position. In addition, the EMA has requested additional preclinical mechanistic studies to better understand these findings. It is also possible that regulatory agencies 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. By a decision on June 15, 2018, the EMA agreed with the PIP for setmelanotide and granted a related deferral. We are required to complete all of the studies included in the PIP by December 2024.

Additionally, setbacks may be caused by new safety or efficacy observations made in clinical trials, including previously unreported adverse events, or AEs. 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 a marketing authorization from the European Commission. If we fail to continue 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 MC4R 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 MC4R pathway deficiencies. As a result, we have had to rely on other available sources to derive clinical prevalence estimates for our target indications. In addition, we have internal genetic sequencing results from 13,567 patients, as of September 2019, with severe obesity that provide another approach to estimating prevalence. 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 MC4R pathway deficiencies based on the following sources and assumptions:

- *POMC Deficiency Obesity.* Our addressable patient population estimate for POMC deficiency obesity is approximately 100 to 500 patients in the United States, with a comparable addressable patient population in Europe. Our estimates are based on:

- 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 obesity is often unavailable and currently is rarely performed;
- our belief, based on discussions with experts in rare diseases, that the number of diagnosed cases could increase several-fold with increased awareness of this deficiency and the availability of new treatments;
- 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
- our internal sequencing yield for POMC deficiency obesity patients (including both POMC and proprotein convertase subtilisin/kexin 1, or PCSK1, gene disorders) of approximately 0.06%.

- *LEPR Deficiency Obesity.* Our addressable patient population estimate for LEPR deficiency obesity is approximately 500 to 2,000 patients in the United States, with a comparable addressable patient population in Europe. Our estimates are based on:
  - epidemiology studies on LEPR deficiency obesity 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);
  - with wider availability of genetic testing expected for LEPR deficiency obesity and increased awareness of new treatments, our belief that up to 40% of patients with these disorders may eventually be diagnosed; and
  - our internal sequencing yield for LEPR deficiency obesity patients of approximately 0.15%.

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 obesity, and (z) our estimated diagnosis rate of up to 40%. In addition, we considered the results of our internal sequencing yields, which support our clinical epidemiology estimates.

- *Bardet-Biedl Syndrome.* Our addressable patient population estimate for BBS 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 BBS 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 patients in the United States. 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 or LEPR Heterozygous Deficiency Obesities, or HET obesity.* Our addressable patient population estimate for patients with high-impact variants (the subset of POMC or LEPR heterozygous patients with loss of function variants such as truncations, frame-shift, and splice variants, as well as well-characterized, published missense variants likely to cause loss-of-function variants of the MC4R pathway, expected to be most responsive to setmelanotide) is approximately greater than 20,000 patients in the United States, with a comparable addressable patient population in Europe. Our estimates are based on:
    - U.S. Census Bureau figures for adults and children, and CDC prevalence numbers for severe adult obese patients (body mass index, or BMI, greater than 40 kg/ m2) and for severe early onset obese children (99th percentile at ages two to 17 years old); and
    - our internal sequencing yield for patients with high-impact heterozygous variants of approximately 0.7%.
- *POMC Epigenetic Disorders.* There is currently no epidemiology data that defines the prevalence of POMC epigenetic disorders.
- *SRC1 Deficiency Obesity.* Our addressable patient population estimate for SRC1 deficiency obesity is approximately greater than 23,000 patients in the United States. This estimate is based on:
    - U.S. Census Bureau figures for adults and children, and CDC prevalence numbers for severe adult obese patients (body mass index, or BMI, greater than 40 kg/ m2) and for severe early onset obese children (99th percentile at ages two to 17 years old); and
    - our internal sequencing yield for SRC1 deficiency obesity patients of approximately 2.5% prior to application of functional and computational filters.
- *SH2B1 Deficiency Obesity.* Our addressable patient population estimate for SH2B1 deficiency obesity is approximately greater than 24,000 patients in the United States. This estimate is based on:
    - U.S. Census Bureau figures for adults and children, and CDC prevalence numbers for severe adult obese patients (body mass index, or BMI, greater than 40 kg/ m2) and for severe early onset obese children (99th percentile at ages two to 17 years old); and
    - our internal sequencing yield for SH2B1 deficiency obesity patients of approximately 1.8% prior to application of functional and computational filters.
- *MC4R Deficiency Obesity.* Our addressable patient population estimate for MC4R deficiency obesity is approximately greater than 10,000 patients in the United States. This estimate is based on:
    - U.S. Census Bureau figures for adults and children, and CDC prevalence numbers for severe adult obese patients (body mass index, or BMI, greater than 40 kg/ m2) and for severe early onset obese children (99th percentile at ages two to 17 years old); and

- our internal sequencing yield for MC4R deficiency obesity patients of approximately 2.0% prior to application of functional filters.

- *Smith-Magenis Syndrome.* Our addressable patient population estimate for Smith-Magenis syndrome is approximately greater than 2,400 patients in the United States. This estimate is based on:

  - published prevalence estimates of one in 25,000 in the United States, which projects to approximately 13,000 people in the United States;

  - published prevalence estimates that approximately 10% of patients with Smith-Magenis syndrome have RAI1 variants that may affect the MC4R pathway and 90% of patients with Smith-Magenis syndrome have 17p11.2 chromosomal deletions which also may affect the MC4R pathway, of which approximately 67% and 13%, respectively, live with obesity; and

  - U.S. Census Bureau figures for total population of adults and children.

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 EU 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 might 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, and suggests that genetic epidemiology estimates of POMC deficiency obesity and LEPR deficiency obesity may be five times higher than clinical epidemiology estimates. 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.

Furthermore, as of September 2019, we collected samples from 13,567 individuals with severe obesity, which yielded 11.7%, or 1,584, genetically-identified individuals with a rare genetic variant of the MC4R pathway and who may be eligible for inclusion in our Phase 2 Basket Study or pivotal Phase 3 clinical trials. Inclusive of these results, our sequencing programs have now sequenced over 25,000 severely obese individuals. We plan to update results from our sequencing activity in 2020. The yields for the indications are outlined above, but then are subject to application of functional and/or computational filters to calculate the prevalence estimates in the United State population. A rarity filter means the specific variant appears in less than 1% of people, and the functional and computational filters help us focus our estimates based on the highest confidence loss-of-function variants. These genetic sequencing results have identified samples from 29 patients with POMC deficiency obesity and LEPR deficiency obesity, which is consistent with our clinical epidemiology estimates.

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 POMC and LEPR deficiency obesities. However, as the clinical epidemiology estimates tend to be lower, to be conservative, we generally reference the clinical epidemiology figures in our descriptions of our target indications.

Defining the exact genetic variants that result in MC4R pathway disorders is complex, so 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 MC4R 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. Patient enrollment may also be adversely affected by competition and other factors.

If the actual number of patients with any of the MC4R 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 have started treating patients six years and older in our trials. Our aim is to gain regulatory approval and labeling for patients six years of age and older. We have only recently received permission from the FDA and other equivalent competent authorities in the EU member states to enroll these younger patients, aged six to eleven, 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 PEG vehicle in the product to carry additional risks in pediatric patients, and we 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 eleven year old patients at the time of the NDA submission for POMC deficiency obesity and LEPR deficiency obesity, if we begin recruiting six to eleven 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 the European Commission in the EU will approve and issue a marketing authorization for setmelanotide for use 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 the European Commission in the EU do not approve or grant marketing authorization for the use of setmelanotide in this population, we will not be permitted to promote the use of setmelanotide for these patients, even if setmelanotide is approved in the United States by the FDA and authorized to be placed on the market in the EU by the European Commission for use in patients twelve and older. Even if approved, the promotion of setmelanotide for uses that are not approved by the FDA or authorized in the EU constitutes off-label promotion. The off-label promotion of medicinal products is prohibited in the United States and EU. Breach of the rules governing the promotion of medicinal products in the United States and EU are subject to administrative enforcement and judicial action, including fines and imprisonment.

While we currently have no knowledge of competitors developing product candidates intended to treat upstream MC4R 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 recently announced positive topline results from an ongoing pivotal Phase 3 clinical trial for setmelanotide for POMC deficiency obesity and LEPR deficiency obesity. These trials are overlapping in timing and duration and we have discussed with regulatory agencies our plan to file one NDA for these two indications, which would have an impact on NDA timing and complexity.

We believe we have demonstrated proof of concept in BBS and Alström syndrome based on prior clinical data, and we completed enrollment of a combined pivotal Phase 3 clinical trial in BBS and Alström syndrome in December 2019, but enrollment of supplemental cohort continues. We believe that the combined BBS and Alström syndrome Phase 3 pivotal clinical trial design will be similar to those for POMC and LEPR deficiency obesity, respectively, but may also include differences most likely due to the larger available patient population for inclusion in a clinical study. There may be other changes as well, including simpler titration schemes, a short placebo-controlled randomized period, and modest differences in our statistical approach due to the different patient populations, the size and combined nature of the study.

We have also initiated Phase 2 clinical trials, referred to as our Basket Study, for POMC and other MC4R pathway heterozygous deficiency obesities and POMC epigenetic disorders. Based on results from our genetic sequencing programs, we intend to expand our Basket Study to include SRC1 deficiency obesity, SH2B1 deficiency obesity, MC4R deficiency obesity and Smith-Magenis syndrome. We anticipate that the Basket Study may be more complex than the Phase 2 clinical trials for which we have achieved proof of concept, and will include larger numbers of subjects to be enrolled. In addition, we anticipate that we will have to define a subset of heterozygous patients for whom setmelanotide will have a clinically meaningful impact, and this may take more patients and more time to develop than other indications for setmelanotide. In March 2019, we announced data for High Impact Het patients (the subset of MC4R pathway heterozygous patients with well-characterized, published, high-impact loss-of-function variants, that we expect to be most responsive to setmelanotide). However, the data from these initial patients is limited and preliminary, and further clinical study is needed to determine if the results in this subset of patients is both robust and consistent.

In addition, the outcome for these new indications is less certain. As our genetic sequencing efforts progress, we expect to add additional new MC4R pathway indications to our Basket Study in the future, and many uncertainties will exist for these new populations as well. Therefore, we believe that a transition from proof of concept to pivotal trials will be longer and more complex for POMC heterozygous deficiency obesity, and POMC epigenetic disorders, and possibly for any additional new indications, due to the greater variety of clinical presentation in those conditions.

Successful completion of our 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.

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 ongoing or planned Phase 3 clinical trials or any other clinical trials we may initiate, or may place a clinical trial on hold or be suspended;
- delays in filing or receiving approvals or an additional investigational new drug application, or 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 or LEPR 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 BBS and Alström syndrome (or any new indications we may study) for many reasons, including the fact that while we may have additional discussions with the FDA regarding clinical trials for these indications, we do not know if the FDA will propose additional changes to our proposed Phase 3 clinical trial design;

- potential difficulties in defining the indication for BBS, (or any new syndromic indications we may study), as there may be discrepancies between the syndromic, or clinical definition of the syndrome, and the genetic confirmation of the indication. For example, one of our syndrome patients without genetic BBS confirmation showed little response to setmelanotide;

- potential difficulties in defining the indications for MC4R pathway heterozygous or epigenetic disorders, as well as for potential new MC4R pathway indications;

- 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, or even any response to treatment, or may not persist in their response to treatment;

- MC4R pathway 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 the need to study larger numbers of patients than for our first two indications, 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;

- patient compliance with or adherence to medication and 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, which might have an important impact on our primary pivotal trial endpoints for responders;

- dose responses may be different in the populations studied and may relate to a 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; and

- development of antibodies to the drug or adjuvants may result in loss of efficacy or safety events.

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 institutional review boards, or 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 applied the same guidance in our Phase 3 clinical trial for setmelanotide in LEPR deficiency obesity and 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 or other equivalent competent authorities in foreign jurisdictions 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 assess 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 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;
- headache;
- effects on mood, depression, anxiety and other psychiatric manifestations; and
- other effects, for which most investigators reported as unrelated to setmelanotide and for which no increased incidence or pattern is currently evident.

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, or SAE, 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. In addition to the SAE described above, there have been a moderate number of additional incidents overall which have led to SAEs in the full development program, which have been determined not to be related to setmelanotide treatment. These have included patients on setmelanotide, as well as patients who were not taking setmelanotide. There has been no pattern to these unrelated serious adverse experiences. There has also been a SAE with

respect to a study participant on setmelanotide in our Phase 3 pivotal study for LEPR deficiency obesity who died in a fatal motor vehicle accident, in which the driver lost control, and our study participant was a passenger. This was determined not to be related to setmelanotide treatment. In addition, one study participant withdrew from our Phase 3 pivotal study for LEPR deficiency obesity before the end of the titration due to mild hypereosinophilia, which was determined not to be related to setmelanotide treatment.

We have also initiated trials of setmelanotide in potential new indications that include patients who might have more serious underlying conditions, such as Alström syndrome and other indications. It is possible that the underlying conditions in these patients, such as congestive heart failure 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 or vary 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, the European Commission and other equivalent competent authorities in foreign jurisdictions may require the addition of a REMS or other specific obligations as a condition for marketing authorization due to the need to limit treatment to rare patient populations, or to address safety concerns;
- we may be required to change the way the product is distributed or administered or change the labeling of the product;
- we may be required to conduct additional studies and clinical trials or comply with other post-market requirements to assess possible serious risks;
- we may be required to conduct long term safety follow-up evaluations, including setting up disease and drug based registries;
- 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, LEPR deficiency obesity and Bardet-Biedl syndrome in both the United States and the EU, and Prader-Willi syndrome and Alström syndrome in the EU, 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.

In the EU, orphan drug designation is granted by the European Commission based on a scientific opinion by the EMA's Committee for Orphan Medicinal Products in relation to medicinal products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than five in 10,000 persons in the EU and in relation to which no satisfactory method of diagnosis, prevention, or treatment has been authorized (or the product would be a significant benefit to those affected). Additionally, designation is granted for products intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the medicinal product in the EU would be sufficient to justify the necessary investment in developing the medicinal product.

In addition to a range of other benefits during the development and regulatory review, orphan medicinal products are, upon grant of marketing authorization, entitled to ten years of exclusivity in all EU member states. Marketing authorization may, however, be granted to a similar medicinal product with the same orphan indication during the ten-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 the similar product is deemed 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.

Grant of orphan designation by the European Commission also entitles the holder of this designation to financial incentives such as reduction of fees or fee waivers. Orphan drug designation must be requested before submitting an application for marketing authorization. Orphan drug designation does not, in itself, convey any advantage in, or shorten the duration of, the regulatory review and authorization process.

We have been granted orphan drug designation for setmelanotide in treating POMC deficiency obesity, LEPR deficiency obesity and BBS in both the United States and the EU. We have been granted orphan designation for setmelanotide in treating Prader-Willi syndrome and Alström syndrome in the EU. There can be no assurance that the

FDA or the European Commission will grant such designation for setmelanotide for other uses. For example, if the FDA were to refuse to recognize all MC4R pathway deficiencies as separate diseases or conditions, the population of patients in the United States with a particular disease or condition, as defined by the FDA, who would be appropriate candidates for setmelanotide could be more than 200,000 or more individuals. In that event, the drug may not qualify for orphan drug designation by the FDA, even if the population of patients with a specific MC4R pathway deficiency for which we seek 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. As discussed above, similar rules apply in the EU.

The FDA Reauthorization Act of 2017 amended the FDCA by codifying 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 law reversed 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 PRIME designation in the EU and Breakthrough Therapy designation for setmelanotide for the treatment of obesity associated with genetic defects upstream of the MC4R in the leptin-melanocortin pathway, which includes POMC deficiency obesity, LEPR deficiency obesity, Bardet-Biedl syndrome and Alström syndrome in the United States, 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 or a marketing authorization in the EU.

The FDA is authorized under the FDCA 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. In addition, the FDA may consider reviewing portions of an NDA before the sponsor submits the complete application, or rolling review. 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. Regulatory standards to demonstrate safety and efficacy must still be met. 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.

The PRIME program was launched by the EMA in 2016. PRIME is intended to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimize development plans and speed up evaluation so these

medicines can reach patients earlier. In late June 2018, setmelanotide was designated as PRIME by the CHMP. Acknowledging that setmelanotide targets an unmet medical need, the EMA offers enhanced support in the development of the medicinal product through enhanced interaction and early dialogue to optimize our development plans and speed up regulatory evaluation in the EU. As part of this designation, the EMA has provided guidance to us concerning the development of setmelanotide. The PRIME designation does not, however, guarantee that the regulatory review process in the EU will be shorter or less demanding. Neither does the PRIME designation guarantee that the European Commission will grant a marketing authorization for setmelanotide.

We may not be able to translate the once-daily 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 once-daily 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 once-daily formulation of setmelanotide into a once-weekly formulation that may 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 once-weekly setmelanotide. This formulation, if successfully developed for setmelanotide, will be delivered subcutaneously, similar to our once-daily 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, with longer studies in process. 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, while we have started consultations with regulatory authorities about the path for approval of the once-weekly formulation, we cannot yet estimate the requirements for non-clinical and clinical data, manufacturing program, time, cost, and probability of success for approval. A medicinal product called Buvidal in the EU and Brixadi in the United States (buprenorphine) that contains the Camurus formulation has been authorized to be marketed in the EU by the European Commission to treat dependence on opioids. In December 2018, Brixadi was granted tentative approval for treatment of Opioid Use Disorder, or OUD, in the United States, subject to expiration of an exclusivity period granted to another product, Sublocade, which is based upon a different formulation of buprenorphine. Excluding this, Camurus formulations have not been approved for any product by the FDA at this time, which further complicates our understanding for the path to approval.

We plan to seek FDA approval of the once-daily formulation in the initial NDA submission for POMC deficiency obesity and LEPR deficiency obesity, and to seek approval of the once-weekly formulation at a later time. While we plan to develop the once-weekly formulation, or to develop other 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 gain approval and utilize the once-daily formulation and/or the once-weekly 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 MC4R 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 have focused our development of setmelanotide as a treatment for obesity caused by certain genetic deficiencies affecting the MC4R 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 & 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 post-market 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' 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 and has provided comments to members of Congress 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.

The FDA recently reiterated its position that an LDT is sufficient for identifying patients in our clinical trials, but the agency also recently indicated that approval of an *in vitro* companion diagnostic device will be needed. *In vitro* companion diagnostic devices, or companion diagnostics, provide information that is essential for the safe and effective use of a corresponding therapeutic product. These companion diagnostics may be co-developed with a device manufacturer or with a laboratory, and generally require FDA approval as well. The FDA stated that absence of complete development of a companion diagnostic would not preclude us from submitting an NDA or preclude the FDA from reviewing it. The FDA also stated that completing development of a companion diagnostic as a post-marketing commitment or a post-marketing requirement is a possibility, assuming that upon review, no issues related to efficacy or safety arise that would necessitate a companion diagnostic at the time of approval. The FDA has indicated it will work with us to identify the least burdensome analytical validation approach to a companion diagnostic for setmelanotide. We are engaged in ongoing discussions with the FDA regarding development of a Class II companion diagnostic.

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 are dependent on the sustained cooperation and effort of third-party collaborators with whom we partner with to develop companion diagnostics. We and our current and 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 current and 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 a companion diagnostic to accurately identify the patients who belong to the target subset, the FDA may require product labeling that limits use to only those patients who express the genetic variants identified by the device. Moreover, even if setmelanotide and a companion diagnostic 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 MC4R pathway, and we and the FDA have agreed on a path to define these variants for approval, which can also be used to categorize new variants as they are identified and that has been used for other diagnostics. These approaches are complex, and the impact on the size of the indicated patients is not certain.

In addition, we intend to continue 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. In addition, the process of conversion of patients with a genetic diagnosis of MC4R pathway disorders to patients receiving treatment is still uncertain and may be complex.

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 in the United States and the EU 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 at risk for adverse experiences and for this, and many other reasons, clinical trials in that population are 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 MC4R pathway disorder is supported primarily on the role of genes, such as MAGEL2 and PCSK1 (also known as PC1), in animal models of obesity. Our results may support that PWS is not an upstream MC4R pathway disorder. Alternatively, other design factors may have influenced the outcome of this trial, and we will be reassessing 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

The successful commercialization of setmelanotide and our other product candidates will depend in part on the extent to which governmental authorities, private health insurers, and other third-party payors provide coverage and adequate reimbursement levels. Failure to obtain or maintain coverage and adequate reimbursement for setmelanotide or our other product candidates, if approved, could limit our ability to market those products and decrease our ability to generate revenue.

Our ability to commercialize setmelanotide or any product candidates successfully will depend in part on the extent to which coverage and reimbursement for these product candidates and related treatments will be available from government authorities, private health insurers and other organizations. 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.

Third-party payors increasingly are challenging prices charged for pharmaceutical products and services. Even if we show improved efficacy or improved convenience of administration with our product candidates, third-party payors may deny or revoke the reimbursement status of our product candidates, if approved, or establish prices for our product candidates at levels that are too low to enable us to realize an appropriate return on our investment. If reimbursement is not available or is available only at limited levels, we may not be able to successfully commercialize setmelanotide or other product candidates, and may not be able to obtain a satisfactory financial return.

No uniform policy for coverage and reimbursement for products exist among third-party payors in the United States. Therefore, coverage and reimbursement for products can differ significantly from payor to payor. As a result, the coverage determination process is often a time-consuming and costly process that may require us to provide scientific and clinical support for the use of setmelanotide to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance. Furthermore, rules and regulations regarding reimbursement change frequently, in some cases on short notice, and we believe that changes in these rules and regulations are likely.

Moreover, increasing efforts by governmental and third-party payors in the United States and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for newly approved products and, as a result, they may not cover or provide adequate payment. We may experience pricing pressures in connection with the sale of setmelanotide or our product candidates due to the trend toward managed health care, the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and biologics and surgical procedures and other treatments, has become intense. As a result, increasingly high barriers are being erected to the entry of new products.

In some foreign countries, particularly in Canada and in the EU member states, the pricing and reimbursement of prescription only medicinal products is subject to strict governmental control which varies widely between countries. In these countries, pricing negotiations with governmental authorities can take six to twelve 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.

As a further step in this direction, on January 31, 2018, the European Commission adopted a proposal for a regulation on HTA. This legislative proposal is intended to boost cooperation among EU member states in assessing health technologies, including new medicinal products, and providing the basis for cooperation at the EU level for joint clinical assessments in these areas. The proposal would permit EU member states to use common HTA tools, methodologies, and procedures across the EU, working together in four main areas, including joint clinical assessment of the innovative health technologies with the most potential impact for patients, joint scientific consultations whereby developers can seek advice from HTA authorities, identification of emerging health technologies to identify promising technologies early, and continuing voluntary cooperation in other areas. Individual EU member states will continue to be responsible for assessing non-clinical (e.g., economic, social, ethical) aspects of health technology, and making decisions on pricing and reimbursement. The European Commission has stated that the role of the draft HTA regulation is not to influence pricing and reimbursement decisions in the individual EU member states. However, this consequence cannot be excluded. The related legislative process is currently ongoing with EU member states divided on the proposal.

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 seek marketing authorization 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. Marketing authorization procedures vary among countries and can involve additional setmelanotide testing and additional administrative review periods. The time required to obtain marketing authorization in other countries might differ from that required to obtain FDA approval. The marketing authorization 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. Grant of marketing authorization in one country does not ensure grant of marketing authorization in another country, but a failure or delay in obtaining marketing authorization in one country may have a negative effect on the regulatory process or commercial activities in others. Failure to obtain marketing authorization in other countries or any delay or other setback in obtaining such authorizations 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 MC4R 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 MC4R 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 complexities of genetic testing, including obtaining genetic results that support patient treatment with setmelanotide;
- 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;
- our ability to increase awareness of these diseases among our target populations through marketing efforts;
- 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 treatments for regulating hunger and hyperphagia related behaviors of patients with POMC deficiency obesity, LEPR deficiency obesity, BBS, Alström syndrome, POMC heterozygous deficiency obesity, POMC epigenetic disorders, SRC1 deficiency obesity, SH2B1 deficiency obesity, MC4R deficiency obesity, or Smith-Magenis syndrome. 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 clinical development for the obesity and hyperphagia caused by upstream MC4R 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 have 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 manufacture our clinical drug supply internally for 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. Our failure or the failure of our CMOs to pass preapproval inspection of the manufacturing facilities of setmelanotide could delay the regulatory approval process. 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 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 which could significantly impact the global supply chain for setmelanotide. With the exception of those on the FDA's drug shortage list or properly imported by individuals, the FDCA prohibits the importation of prescription drug products 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 various third parties for the manufacture of setmelanotide and intend to continue to do so in the future. We have entered into process development and manufacturing service agreements with three CMOs: Corden Pharma Brussels S.A, or Corden (formerly Peptisyntha SA prior to its acquisition by Corden), PolyPeptide Group, Baine L'Alleud, or PPL, and Neuland Laboratories, in connection with certain process development and manufacturing services for regulatory starting materials and/or drug substance, or API 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 drug product. Under our agreements, we pay these third parties for services in accordance with the terms of mutually agreed upon work orders, which we 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 other company materials and products may affect the regulatory clearance of our CMOs' facilities generally. In addition, satisfying the regulatory requirements for production of setmelanotide with multiple suppliers, while assuring more robust drug availability in the future, adds additional complexity and risk to regulatory approval. 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.

Similar rules apply in the EU. Any brand name we propose for setmelanotide in the EU must be approved by the EMA. The objective of the assessment conducted by the EMA is to ensure that there is no risk that the proposed brand name could create a public-health concern or potential safety risk. In particular the proposed brand name should not convey misleading therapeutic or pharmaceutical connotations; be misleading with respect to the composition of the product; or be liable to cause confusion with the brand name of an existing medicinal product in print, handwriting or speech. If the EMA 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 be acceptable to the EMA, qualify under applicable trademark laws and not infringe the existing rights of third parties.

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. Recent legislation enacted by Congress created, among other things, new causes of action against innovator companies that refuse to offer samples of drugs for purposes of testing and developing generic or biosimilar products or to allow companies to participate in a shared Risk Evaluation and Mitigation Strategy (REMS). 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.

In the EU, the grant of orphan designation for setmelanotide means that this medicinal product would be entitled, upon grant of marketing authorization by the European Commission, to ten years of exclusivity in all EU member states. Marketing authorization may, however, be granted to a similar medicinal product with the same orphan indication during the ten year period if we are unable to supply sufficient quantities of setmelanotide. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if the similar product is deemed safer, more effective or otherwise clinically superior to setmelanotide. 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 setmelanotide is sufficiently profitable not to justify maintenance of market exclusivity.

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, LEPR deficiency obesity, Bardet-Biedl syndrome and Alström syndrome. 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 MC4R pathway, including POMC deficiency obesity, LEPR deficiency obesity, BBS and Alström syndrome, 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 resources. 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 three Phase 3 clinical trials underway, one each for the treatment of POMC deficiency obesity and LEPR deficiency obesity, and a third combined Phase 3 trial for BBS and Alström syndrome. We recently reported topline data in our Phase 3 clinical trials for the treatment of POMC deficiency obesity and LEPR deficiency obesity and based on these results, we intend to file an NDA with the FDA in the first quarter of 2020. Under our current development program, we are conducting 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 also received FDA comments that indicate the Phase 3 program for LEPR deficiency obesity can be similar to POMC deficiency obesity and are conducting our Phase 3 trial for LEPR deficiency obesity in a similar way based in part on those comments. Similarly, the preliminary FDA advice on the design of the BBS 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, the design for any placebo-controlled aspect of the trial, as well as other factors that could impact on the ability of the trial to support registration.

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 have agreed with the FDA, and implemented in our pivotal studies, 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, Spain and the United Kingdom for POMC deficiency obesity. We are also conducting this trial in the United States and 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 June 2018, setmelanotide was designated as PRIME by the CHMP. Acknowledging that setmelanotide targets an unmet medical need, the EMA offers enhanced support in the development of the medicinal product through interaction and early dialogue to optimize our development plans and speed up regulatory evaluation in the EU. As part of this designation, the EMA has provided us with guidance concerning the development of setmelanotide. The PRIME designation does not, however, guarantee that the regulatory review process in the EU will be shorter or less demanding. Neither does the PRIME designation guarantee that the European Commission will grant a marketing authorization for setmelanotide.

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 trial in the United States. We have not obtained EMA scientific advice for the LEPR deficiency obesity indication, nor have we obtained EMA scientific advice for the BBS or Alström syndrome indications, except in the more general setting of our PRIME discussions.

Given the orphan status of setmelanotide for the treatment of POMC deficiency obesity in the EU the application for marketing authorization for a POMC deficiency obesity indication must be submitted via the centralized procedure. In November 2018, we obtained orphan designation in the EU for setmelanotide for the treatment of LEPR deficiency obesity.

In addition, we have submitted a PIP for setmelanotide to the EMA Pediatric Committee, or PDCO, in 2017. By a decision in June 2018, the EMA formally accepted 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 in a timely manner. Similar to the United States, we are subject to comprehensive regulatory oversight by 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 manage our Phase 3 clinical trials such that if the clinical trials are successful, we can file an NDA for POMC deficiency obesity and LEPR deficiency obesity in the United States in the first quarter of 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.

In addition, obtaining FDA 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 MC4R 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 AEs 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 may not consider that our diagnostic strategy supports approval;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may decide that additional assays or data to understand any risks for anti-drug antibodies may need to be available for approval;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may decide that the toxicology program, including any parts of carcinogenicity studies that are filed, do not meet the requirements for approval;

- 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, or in the commercial production of setmelanotide to support product approval;

- 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;

- we plan to request the right to submit portions of the NDA before all portions are complete, a process known as rolling review, but even if FDA grants rolling review, the review clock does not begin until the entire NDA is complete, and FDA may request additional information before deeming the NDA to be complete;

- if any when our NDA is approved, we may be required to conduct additional studies and clinical trials or other post-market requirements to assess possible serious risks;

- 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 agencies 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 marketing authorization procedure varies among countries and can involve additional testing. The time required to obtain marketing authorization may differ substantially from that required to obtain FDA approval. The marketing authorization 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 marketing authorization from competent authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure grant of marketing authorization by competent authorities in other countries or jurisdictions, and grant of marketing authorization by one competent authority outside the United States does not ensure grant of marketing authorization by competent authorities in other countries or jurisdictions or by the FDA. We may not be able to file for marketing authorizations and may not receive necessary marketing authorization to commercialize setmelanotide in any market. Additionally, the United Kingdom's withdrawal from the EU, commonly referred to as Brexit, has resulted in the relocation of the EMA from the United Kingdom to the Netherlands. This relocation has caused, and may continue to cause, disruption in the administrative and medical scientific links between the EMA and the U.K. Medicines and Healthcare products Regulatory Agency, including delays in granting clinical trial authorization or marketing authorization, disruption of importation and export of active substance and other components of new drug formulations, and disruption of the supply chain for clinical trial product and final authorized formulations. The cumulative effects of the disruption to the regulatory framework may add considerably to the development lead time to marketing authorization and commercialization of setmelanotide in the EU and/or the United Kingdom. Any delay in obtaining, or an inability to obtain, any marketing authorization, 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 marketing authorization 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 European Commission, 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. Advertising and promotional materials must comply with the FDCA and implementing regulations, and are subject to FDA oversight and post-marketing reporting obligations, in addition to other potentially applicable federal and state laws. 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. 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. The holder of an approved NDA also must submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process, or adding new manufacturers.

Manufacturers of drug products and their facilities may be subject to payment of application and program fees and 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 AEs of unanticipated severity or frequency, or problems with the facility where setmelanotide is manufactured or disagrees with the promotion, marketing or labeling of the product, 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;
- vary, 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.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize our product candidates and adversely affect our business, financial condition, results of operations and prospects.

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.

In addition, a sponsor’s responsibilities and obligations under the FDCA and FDA regulations, and those of equivalent foreign regulatory agencies, may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any regulatory approval that we may have obtained and we may not achieve or sustain profitability, which would materially and adversely affect our business, financial condition, results of operations and prospects.

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,

revocation 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, AE 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, and continue to be, 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 Reconciliation Act of 2010, or collectively the ACA. The ACA substantially changed the way healthcare is financed by both governmental and private insurers, and significantly affects the U.S. pharmaceutical industry. 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 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, revising the “average manufacturer price” definition, and extending rebate liability from fee-for-service Medicaid utilization to include the utilization of Medicaid managed care organizations as well as Medicaid managed care;

- expansion of the list of entity types eligible for participation in the Public Health Service 340B drug pricing program, or the 340B program, to include certain free-standing cancer hospitals, critical access hospitals, rural referral centers, and sole community hospitals, but exempting “orphan drugs” from the 340B ceiling price requirements for these covered entities;

- establishment of the Medicare Part D coverage gap discount program requiring manufacturers to provide a then 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; and

- establishment of 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 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 2029. 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.

Certain provisions of the ACA have been subject to judicial challenges as well as efforts to repeal or replace them or to alter their interpretation or implementation. For example, the Tax Cuts and Jobs Act enacted on December 22, 2017, eliminated the tax-based 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," effective January 1, 2019. Further, the Bipartisan Budget Act of 2018, or BBA of 2018, among other things, amended the Medicare statute, effective January 1, 2019, to reduce the coverage gap in most Medicare drug plans, commonly known as the "donut hole" by raising the manufacturer discount under the Medicare Part D coverage gap discount program to 70%. Additional legislative changes, regulatory changes, and judicial challenges related to the ACA remain possible. It is unclear how the ACA and its implementation, as well as efforts to repeal or replace, or invalidate, the ACA, or portions thereof, will affect our business. It is possible 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 this Medicare quality payment program will impact overall physician reimbursement. The cost 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. There have been several Congressional inquiries and proposed bills and regulatory initiatives 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. For example, the Trump Administration has considered exercising its demonstration authority to test an alternative Medicare Part B drug payment methodology with respect to certain Medicare Part B drugs that is tied to international pricing of such drugs. Any specific reforms that may be enacted or implemented remain uncertain, both as to their substance and timing, and may affect a broad range of public policy considerations, including the Medicare and Medicaid programs and the FDA regulatory regime.

We expect that these and other healthcare reform measures that may be adopted in the future may result in more rigorous coverage and payment 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. For more details concerning the risks related to pricing and reimbursement in the EU, please refer to the discussion in the risk factor "*The successful commercialization of setmelanotide and our other product candidates will depend in part on the extent to which governmental authorities, private health insurers, and other third-party payors provide coverage and adequate reimbursement levels. Failure to obtain or maintain coverage and adequate reimbursement for setmelanotide or our other product candidates, if approved, could limit our ability to market those products and decrease our ability to generate revenue*" in this Annual Report on Form 10-K.

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 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.

The ACA made significant changes to the Medicaid Drug Rebate Program, as described under the risk factor "*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*," above. Congress could enact additional legislation that further increases Medicaid drug rebates or other costs and charges associated with participating in the Medicaid Drug Rebate Program. Additional legislation or the issuance of regulations relating to the Medicaid Drug Rebate Program could have a material adverse effect on our results of operations.

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, which is administered by the Health Resources and Services Administration, or HRSA, 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.

HRSA issued a final regulation regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities, which became effective on January 1, 2019. It is currently unclear how HRSA will apply its enforcement authority under the new regulation. HRSA also has implemented reporting requirement pursuant to which participating manufacturers are required to report the 340B ceiling prices for their drugs to HRSA every quarter. 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.

Pricing and rebate calculations vary among products and programs. The calculations are complex and are often subject to interpretation by us, governmental or regulatory agencies, and the courts. If we participate in the Medicaid Drug Rebate Program and consequently the 340B program, we could be held liable for errors associated with our submission of pricing data. In addition to retroactive Medicaid rebates and the potential for 340B program refunds, if we are found to have knowingly submitted false average manufacturer price or best price information to the government, we may be liable for significant civil monetary penalties per item of false information. Civil monetary penalties can also be applied if we are found to have charged 340B covered entities more than the statutorily mandated ceiling price. Our failure to submit monthly/quarterly average manufacturer price and best price data on a timely basis could result in a significant civil monetary penalty per day for each day the information is late beyond the due date. Such failure also could be grounds for CMS to terminate our Medicaid drug rebate agreement, pursuant to which we would be participating in the Medicaid program. In the event that CMS terminates our rebate agreement, no federal payments would be available under Medicaid or Medicare Part B for our covered outpatient drugs.

CMS and the Department of Health & Human Services Office of Inspector General have pursued manufacturers that were alleged to have failed to report these data to the government in a timely manner. Governmental agencies may also make changes in program interpretations, requirements or conditions of participation, some of which may have implications for amounts previously estimated or paid. If we participate in the Medicaid Drug Rebate Program and consequently the 340B program, we cannot assure you that our submissions will not be found to be incomplete or incorrect.

In order to be eligible to have our products that we successfully commercialize paid for with federal funds under the Medicaid and Medicare Part B programs 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).

The FCP is based on the Non-Federal Average Manufacturer Price, or Non-FAMP, which we would be required to calculate and report to the VA on a quarterly and annual basis. Pursuant to applicable law, knowing provision of false information in connection with a Non-FAMP filing can subject a manufacturer to significant civil monetary penalties for each item of false information. The FSS pricing and contracting obligations also contain extensive disclosure and certification requirements.

If we successfully commercialize our products, we also would participate in the Tricare Retail Pharmacy program, under which we would be required to pay quarterly rebates on utilization of innovator products that are dispensed through the Tricare Retail Pharmacy network to Tricare beneficiaries. The rebates are calculated as the difference between the annual Non-FAMP and FCP. We would be required to list our innovator products on a Tricare Agreement in order for them to be eligible for DOD formulary inclusion. If we overcharge the government in connection with our FSS contract or Tricare Agreement, whether due to a misstated FCP or otherwise, we would be required to refund the difference to the government. Failure to make necessary disclosures and/or to identify contract overcharges could result in allegations against us under the False Claims Act and other laws and regulations. Unexpected refunds to the government, and responding to a government investigation or enforcement action, would be expensive and time-consuming, and could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

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 MC4R 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 and privacy 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, substantial 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 healthcare Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, or receiving remuneration, (anything of value), 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, formulary managers, and patients 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 exceptions and regulatory safe harbors to the federal Anti-Kickback Statute protecting certain common business arrangements and activities from prosecution or regulatory sanctions, the exceptions 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 or patients as consultants, advisors, or speakers, may be subject to scrutiny if they do not fit squarely within an exception 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 and patient support programs. In October 2019, the federal government published a proposed regulation creating new safe harbors for, among other things, certain value-based arrangements and patient engagement tools, and that modifies and clarifies the scope of existing safe harbors for warranties and personal service agreements. The impact of the proposed regulation on our current or contemplated operations is not clear even if the proposed regulation is finalized.

- 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. Such private individuals may share in amounts paid by the entity to the government in recovery or settlement. 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. False Claims Act liability is potentially significant in the healthcare industry because the statute provides for treble damages and significant mandatory penalties per false or fraudulent claim or statement for violations. Because of the potential for large monetary exposure, healthcare and pharmaceutical companies often resolve allegations without admissions of liability for significant and material amounts to avoid the uncertainty of treble damages and per claim penalties that may be awarded in litigation proceedings. Settlements may require companies to enter into corporate integrity agreements with the government, which may impose substantial costs on companies to ensure compliance. 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, including private third-party payors, and also imposes obligations, with respect to safeguarding the privacy, security and transmission of individually identifiable health information. Penalties for failure to comply with a requirement of HIPAA vary significantly and include civil monetary penalties as well as criminal penalties for knowingly obtaining or disclosing individually identifiable health information in violation of HIPAA. The criminal penalties increase if the wrongful conduct involves false pretenses or the intent to sell, transfer or use identifiable health information for commercial advantage, personal gain or malicious harm. HIPAA also 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. Similar to the federal healthcare Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it to have committed a violation. Pharmaceutical and other healthcare companies also are subject to state laws governing the privacy and security of health, genetic, sensitive condition and personally identifiable information, many of which enable a state attorney general to bring actions and provide private rights of action to consumers as enforcement mechanisms. There is also heightened sensitivity for minors' information, which may be subject to additional protections. Federal regulators, state attorneys general, and plaintiffs' attorneys have been and will likely continue to be active in this space.

- The federal Physician Payments Sunshine Act, 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 for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report annually to the United States Department of Health and Human Services, Centers for Medicare and Medicaid Services, information related to physicians (defined to include doctors, dentists, optometrists, podiatrists, and chiropractors) and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Beginning in 2022, applicable manufacturers also will be required to report information regarding payments and transfers of value provided to physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, and certified nurse-midwives. Manufacturers must submit reports 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, including private insurers. 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 individual 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. Some states require the posting of information relating to clinical studies and their outcomes. Other states and cities require identification or licensing of sales representatives. In addition, several states require pharmaceutical companies to implement compliance programs or marketing codes of conduct.

- Similar restrictions are imposed on the promotion and marketing of medicinal products in the EU member states and other countries, including restrictions on interactions with healthcare professionals and requirements for public disclosure of payments made to physicians. Laws (including those governing promotion, marketing and anti-kickback provisions), industry regulations and professional codes of conduct often are strictly enforced. Even in those countries where we may decide not to directly promote or market our products, inappropriate activity by our international distribution partners could have implications for us.

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. The BBA 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, privacy, or other healthcare laws and regulations. If our operations, including our engagements with healthcare professionals, researchers and patients, or our disease awareness and/or patient identification initiatives including genetic testing programs, or anticipated activities to be conducted by our field teams, 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 costly investigations, significant civil, criminal and administrative monetary penalties, imprisonment, damages, fines, disgorgement, exclusion from government funded healthcare programs, such as Medicare and Medicaid, contractual damages, diminished profits and future earnings, and the curtailment or restructuring of our operations, any of which could substantially disrupt our operations or financial results. 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 generate negative publicity, which could harm our financial condition 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, substantial civil penalties, reputational harm and diminished profits and future earnings*" of this Annual Report on Form 10-K.

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, for example, 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, state genetic privacy laws, and federal and state consumer protection laws, including, for example, Section 5 of the Federal Trade Commission Act of 1914, as amended, and the CCPA, govern the collection, use, and disclosure and protection of certain 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. In addition, state laws govern the privacy and security of health, research and genetic information in specified circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. Some of our research activities involve minors, which may be subject to additional laws and can require specialized consent processes, privacy protections, and compliance procedures.

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 AE 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.

Following a national referendum and enactment of legislation by the government of the United Kingdom, the United Kingdom formally withdrew from the EU on January 31, 2020 and entered into a transition period during which it will continue its ongoing and complex negotiations with the EU relating to the future trading relationship between the parties. Significant political and economic uncertainty remains about whether the terms of the relationship will differ materially from the terms before withdrawal, as well as about the possibility that a so-called "no deal" separation will occur if negotiations are not completed by the end of the transition period.

These developments have created significant uncertainty about the future relationship between the United Kingdom and the EU. Lack of clarity about future U.K. laws and regulations as the United Kingdom determines which EU-derived laws and regulations to replace or replicate as part of a withdrawal, including financial laws and regulations, tax and free trade agreements, intellectual property rights, supply chain logistics, environmental, health and safety laws and regulations, immigration laws and employment laws, could further decrease foreign direct investment in the United Kingdom, increase costs, depress economic activity and restrict our access to capital. These developments, or the perception that any of them could occur, have had and may continue to have a significant adverse effect on global economic conditions and the stability of global financial markets, and could significantly reduce global market liquidity and restrict the ability of key market participants to operate in certain financial markets. Asset valuations, currency exchange rates and credit ratings may be especially subject to increased market volatility. Any of these factors could have a significant adverse effect on our business, financial condition, results of operations and prospects.

Further, the United Kingdom's withdrawal from the EU has resulted in the relocation of the EMA from the United Kingdom to the Netherlands. This relocation has caused, and may continue to cause, disruption in the administrative and medical scientific links between the EMA and the U.K. Medicines and Healthcare products Regulatory Agency, including delays in granting clinical trial authorization or marketing authorization, disruption of importation and export of active substance and other components of new drug formulations, and disruption of the supply chain for clinical trial product and final authorized formulations. The cumulative effects of the disruption to the regulatory framework may add considerably to the development lead time to marketing authorization and commercialization of products in the EU and/or the United Kingdom.

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 our executive leadership team. 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.

In January 2020, Keith M. Gottesdiener, M.D., resigned as our Chief Executive Officer and President and as a member of our board effective upon the earlier of (i) the planned NDA filing during the first quarter of 2020, (ii) the start date of a new Chief Executive Officer of the Company, (iii) March 31, 2020, (iv) the effective date of termination of his employment without Cause as defined in his employment agreement dated September 13, 2017 and (v) a termination by Dr. Gottesdiener of his employment on account of material breach of the separation agreement dated January 6, 2020. We are searching for a new Chief Executive Officer but may face challenges in finding a suitable candidate, and we may face risks related to this and any other transitions in our executive leadership team.

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.

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, regulatory investigations, enforcement actions and lawsuits.

In the ordinary course of our business, we collect and store sensitive data, including intellectual property, our proprietary business information and that of our suppliers, as well as personally identifiable information of employees. Similarly, our third-party CROs, CMOs and other contractors and consultants possess certain of our sensitive data. The secure maintenance of this information is material to our operations and business strategy. Despite the implementation of security measures, our internal computer systems and those of our third-party CROs, CMOs and other contractors and consultants are vulnerable to attacks by hackers, damage from computer viruses, unauthorized access, breach due to

employee error, malfeasance or other disruptions, natural disasters, terrorism and telecommunication and electrical failures. Any such attack, incident or breach could compromise our networks and the information stored there could be accessed, publicly disclosed, lost, corrupted or stolen. The legislative and regulatory landscape for privacy and data protection continues to evolve, and there has been an increasing amount of focus on privacy and data protection issues with the potential to affect our business, including recently enacted laws in a majority of states requiring security breach notification, some also require implementation of reasonable security measures and provide a private right of action in the event of a breach. Costs of breach response, mitigation, investigation, remediation, notice and ongoing assessments can be considerable. Thus, any access, disclosure, damage or other loss of information, including our data being breached at our partners or third-party providers, could result in legal claims or proceedings and liability under state, federal and international privacy laws, disruption of our operations, and damage to our reputation, which could adversely affect our business.

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 or other product candidates 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 candidates, or inappropriate disclosure of confidential or proprietary information, we could incur liabilities and the further development of setmelanotide and our product candidates 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

Our directors and executive officers and their affiliated entities own a significant percentage of our stock and, if they choose to act together, will be able to exert significant influence over matters subject to stockholder approval.

Our executive officers and directors and their respective affiliates, in the aggregate, hold shares representing approximately 18.1% of our outstanding voting stock as of December 31, 2019. As a result, if these stockholders were to choose to act together, they would be able to significantly influence all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these stockholders could significantly influence elections of directors, any 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 began trading on the Nasdaq Global Market in October 2017 and we can provide no assurance that we will be able to continue 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 stock 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 or EMA 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 have broad discretion in how we use the proceeds from our June 2018 and October 2019 public offerings. 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 our June 2018 and October 2019 public offerings. 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 the completion of our combined Phase 3 clinical trial for BBS and Alström syndrome, the development of setmelanotide through our Phase 2 proof of concept Basket Study for POMC heterozygous, POMC epigenetic disorders, SRC1 deficiency obesity, SH2B1 deficiency obesity, MC4R deficiency obesity and Smith-Magenis 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 on or after December 31, 2018 are not subject to expiration. NOLs arising in taxable years beginning on or after December 31, 2018 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, 2019, we had approximately $268.0 million and $241.3 million of unused federal and state carryforwards of NOLs, respectively, and approximately $6.4 million and $1.9 million of unused federal and state carryforwards of research tax credits, respectively. Of the federal NOL carryforwards at December 31, 2019, $194.8 million can be carried forward indefinitely. Additionally, as of December 31, 2019, we had federal orphan drug credits related to qualifying research of $6.9 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. As of December 31, 2019, we have 43,996,753 shares of common stock outstanding.

The holders of approximately 7.9 million shares of our common stock, or approximately 18% of our total outstanding common stock as of December 31, 2019, are entitled to rights with respect to the registration of their shares under the Securities Act of 1933, as amended, or 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.

Even after we no longer qualify as an emerging growth company, we may still qualify as a "smaller reporting company" if the market value of our common stock held by non-affiliates is below $250 million (or below $700 million if our annual revenue is less than $100 million) as of June 30 in any given year, which would allow us to take advantage of certain scaled disclosure requirements.

Pursuant to Section 404, 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 continue to achieve compliance with Section 404, we continue to 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 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 securities or industry analysts do not continue to 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 depends 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. If we lose securities or industry analysts coverage of our company, the trading price for our stock would be negatively impacted. 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, our management will continue to devote substantial time to new compliance initiatives and corporation governance policies, and we will need to hire additional qualified accounting and financial personnel with appropriate public company experience.

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, 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 and we will need to continue to hire additional accounting and financial personnel with appropriate public company experience and technical accounting knowledge. 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. 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.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our corporate headquarters are located in Boston, Massachusetts, where we lease approximately 13,600 square feet of office space pursuant to lease agreements expiring in May 2025, with a five-year renewal option to extend the lease. This facility houses our research, clinical, regulatory, commercial and administrative personnel. See Note 9 to our audited consolidated financial statements included in this report for additional information about this lease.

We believe that our existing facilities are adequate for our near-term needs, but if we need additional space as we grow and expand our operations. We believe that suitable additional or alternative office space would be available as required in the future on commercially reasonable terms.

Item 3. Legal Proceedings

We are not currently a party to any material legal proceedings.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

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.

Holders of Common Stock

As of February 28, 2020, there were 20 holders of record of our common stock. This number does not reflect beneficial owners whose shares are held in street name.

Securities Authorized for Issuance Under Equity Compensation Plans

Information regarding our equity compensation plans and the securities authorized for issuance thereunder is set forth herein under Part III, Item 12 below.

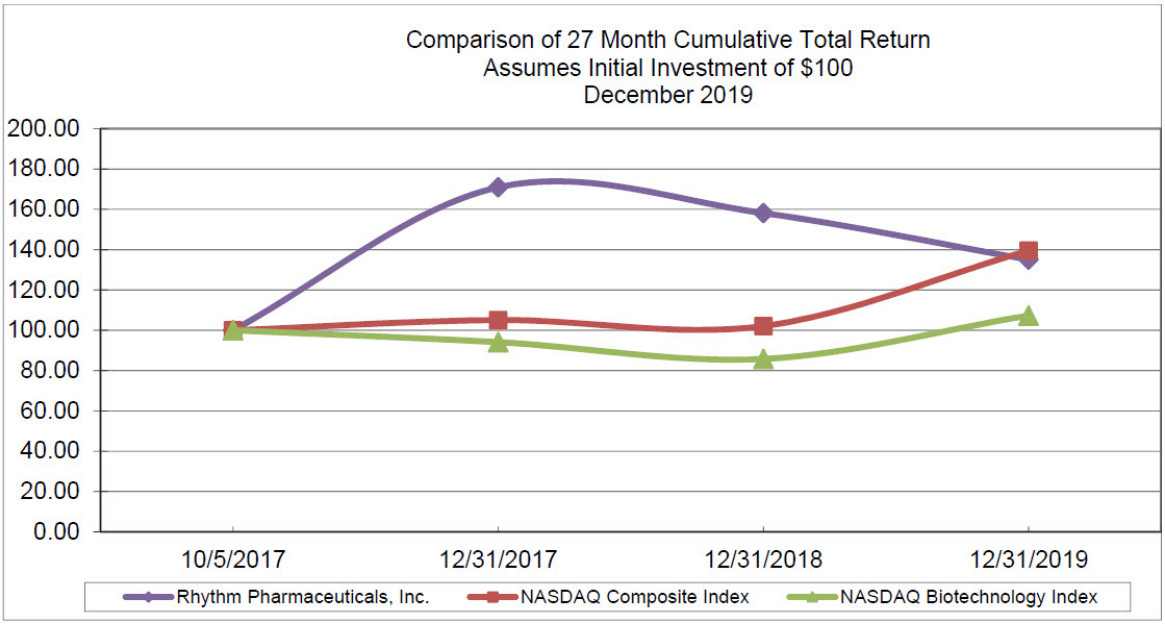
Dividend Policy

We have never declared or paid any cash dividends on our common stock or any other securities. We anticipate that we will retain all available funds and any future earnings, if any, for use in the operation of our business and do not anticipate paying cash dividends in the foreseeable future. In addition, future debt instruments may materially restrict our ability to pay dividends on our common stock. Payment of future cash dividends, if any, will be at the discretion of the board of directors after taking into account various factors, including our financial condition, operating results, current and anticipated cash needs, the requirements of current or then-existing debt instruments and other factors the board of directors deems relevant.

Performance Graph

This graph is not "soliciting material," is not deemed "filed" with the SEC and is not to be incorporated by reference into any filing of Rhythm Pharmaceuticals, Inc. under the Securities Act or the Securities Exchange Act of 1934, as amended, or the Exchange Act, whether made before or after the date hereof and irrespective of any general incorporation language in any such filing.

The following graph shows the total stockholder return of an investment of $100 in cash at market close on October 5, 2017 (the first day of trading of our common stock) through December 31, 2019 for (1) our common stock, (2) the Nasdaq Composite Index (U.S.) and (3) the Nasdaq Biotechnology Index. Pursuant to applicable Securities and Exchange Commission rules, all values assume reinvestment of the full amount of all dividends, however no dividends have been declared on our common stock to date. The stockholder return shown on the graph below is not necessarily indicative of future performance, and we do not make or endorse any predictions as to future stockholder returns.



Recent Sales of Unregistered Securities

None.

Use of Proceeds from Registered Securities

Shares of our common stock began trading on the Nasdaq Global Market on October 5, 2017. The offer and sale of all the shares in the initial public offering, or IPO, were registered under the Securities Act pursuant to a registration statement on Form S-1 (File No. 333-220337), which was declared effective by the SEC on October 4, 2017. As of December 31, 2019, we estimate that we have used all of the net proceeds from the IPO to fund the clinical development of setmelanotide and for working capital, capital expenditures and other general corporate purposes.

We issued shares of our common stock on the Nasdaq Global Market on June 25, 2018. The offer and sale of all the shares in the public offering were registered under the Securities Act pursuant to a registration statement on Form S-1 (File No. 333-225700), which was declared effective by the SEC on June 20, 2018.

We issued shares of our common stock on the Nasdaq Global Market on October 18, 2019. The offer and sale of all the shares in the public offering were registered under the Securities Act pursuant to a shelf registration statement on Form S-3 (File No. 333-228323), which automatically became effective upon filing with the SEC on November 9, 2018.

There has been no material change in the planned use of proceeds from our public offerings as described in the Prospectuses filed with the SEC pursuant to Rule 424(b) under the Securities Act on October 4, 2017, June 20, 2018 and October 18, 2019.

Issuer Purchases of Equity Securities

Not applicable.

Item 6. Selected Financial Data

You should read the following selected consolidated financial data in conjunction with our consolidated financial statements and the related notes which are included elsewhere in this Annual Report on Form 10-K and the "Management's Discussion and Analysis of Financial Condition and Results of Operations" section of this Annual Report on Form 10-K. We have derived the consolidated statement of operations data for the years ended December 31, 2019, 2018 and 2017, and the consolidated balance sheet data as of December 31, 2019 and 2018, from our audited consolidated financial statements, which are included elsewhere in this Annual Report.

Our financial statements for the years ended December 31, 2016 and 2015, include allocations of costs from certain shared functions provided to us by the Predecessor Company, as defined below. 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 Annual Report 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. We were organized in February 2013. Prior to our organization and a corporate reorganization, we were part of Rhythm Pharmaceuticals, Inc., a Delaware corporation which was organized in November 2008 and commenced active operations in 2010. We refer to this corporation as the Predecessor Company.

Our historical results for any prior period are not necessarily indicative of results to be expected for any future period. Amounts below are in thousands, except share and per share data.

	Year Ended December 31, 2019	Year Ended December 31, 2018	Year Ended December 31, 2017	Year Ended December 31, 2016	Year Ended December 31, 2015
Operating expenses:					
Research and development	$ 109,450	$ 50,337	$ 22,894	$ 19,594	$ 7,148
Selling, general, and administrative	36,550	28,080	9,518	6,311	3,425
Total operating expenses	146,000	78,417	32,412	25,905	10,573
Loss from operations	(146,000)	(78,417)	(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	5,271	4,353	566	33	—
Total other income (expense), net	5,271	4,353	(1,297)	33	(500)
Net loss	$ (140,729)	$ (74,064)	$ (33,709)	$ (25,872)	$ (11,073)
Net loss attributable to common stockholders	$ (140,729)	$ (74,064)	$ (37,582)	$ (29,074)	$ (12,000)
Net loss attributable to common stockholders per common share, basic and diluted	$ (3.86)	$ (2.39)	$ (2.83)	$ (2.85)	$ (1.18)
Weighted-average common shares outstanding, basic and diluted	36,422,450	31,004,047	13,267,960	10,196,292	10,196,292

	December 31,				
	2019	2018	2017	2016	2015
Balance Sheet Data:					
Cash and cash equivalents	$ 62,294	$ 49,542	$ 34,236	$ 6,540	$ 34,869
Short-term investments	230,165	202,519	113,846	3,997	—
Working capital	277,987	245,107	143,951	6,444	30,218
Total assets	308,523	260,210	151,736	12,339	37,275
Series A Convertible Preferred Stock	—	—	—	40,000	40,000
Accumulated deficit	(325,331)	(184,602)	(110,252)	(76,543)	(50,671)
Total stockholders' equity (deficit)	$ 281,020	$ 246,256	$ 144,788	$ (32,703)	$ (7,999)

Item 7. 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 related notes appearing elsewhere in this Annual Report on Form 10-K, or this Annual Report. In addition to historical information, this discussion and analysis contains forward-looking statements that involve risks, uncertainties and assumptions. Our actual results may differ materially from those anticipated in these forward-looking statements as a result of certain factors. We discuss factors that we believe could cause or contribute to these differences below and elsewhere in this report, including those set forth under Item 1A. "Risk Factors" and under "Cautionary Note Regarding Forward-Looking Statements" in this Annual Report. Discussion and analysis of our 2017 fiscal year specifically, as well as the year-over-year comparison of our 2018 financial performance to 2017, are located in Part II, Item 7 - Management's Discussion and Analysis of Financial Condition and Results of Operations in our Annual Report on Form 10-K for the fiscal year ended December 31, 2018, filed with the SEC on March 8, 2019, which is available on the SEC's website at www.sec.gov and incorporated herein by reference.

Overview

We are a late-stage biopharmaceutical company focused on the development and commercialization of therapeutics for the treatment of rare genetic disorders which are characterized by severe early-onset obesity and an unrelenting hunger or hyperphagia. Our lead product candidate is setmelanotide, a potent melanocortin-4 receptor, or MC4R, agonist 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 MC4R pathway deficiencies. MC4R 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 several single gene-related, or monogenic, MC4R pathway deficiencies: pro-opiomelanocortin, or POMC, deficiency obesity; leptin receptor, or LEPR, deficiency obesity; Bardet-Biedl syndrome, or BBS; Alström syndrome; POMC or LEPR heterozygous deficiency obesity; steroid receptor coactivator 1, or SRC1, deficiency obesity; SH2B adapter protein 1, or SH2B1, deficiency obesity; MC4R deficiency obesity and Smith-Magenis syndrome, as well as additional disorders as part of investigator-initiated protocols. There are currently no effective or approved treatments for these MC4R pathway-related disorders. We believe that the MC4R 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 recently reported positive topline Phase 3 data in POMC deficiency obesity and LEPR deficiency obesity, and have previously demonstrated proof of concept in Phase 2 clinical trials in BBS and Alström syndrome. In these four genetic disorders of extreme and unrelenting appetite and obesity, setmelanotide has 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 MC4R in the leptin melanocortin pathways. The Breakthrough Therapy designation currently covers indications for

POMC deficiency obesity, LEPR deficiency obesity, BBS and Alström syndrome. We plan to complete our NDA submission for POMC deficiency obesity and LEPR deficiency obesity before the end of the first quarter of 2020.

We have demonstrated proof of concept in our Phase 2 clinical trial in BBS and 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 discussions with the FDA, we initiated this Phase 3 trial in December 2018 and we completed enrollment in December 2019 and expect to report topline data at the end of 2020 or early in the first quarter of 2021. We have an ongoing Phase 2 clinical trial in MC4R pathway heterozygous deficiency obesity and POMC epigenetic disorders that we expanded in the second half of 2019 to include the following additional indications: SRC1 deficiency obesity, SH2B1 deficiency obesity, MC4R deficiency obesity and Smith-Magenis syndrome. We reported preliminary results in MC4R pathway heterozygous deficiency obesity in March 2019 and expect to report additional data in this indication in 2020. In total, approximately 450 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.

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 have assumed 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. We expect to file an investigational new drug application, or IND, for RM-853 in 2020.

We currently have 70 employees. Of these employees, 46 are engaged in research and development activities, 10 are engaged in pre-commercialization activities and 14 are engaged in support administration, including finance, IT and human resources. In the near-term, we expect to expand our research, clinical development and commercial personnel, in particular, and will incur increased expenses as a result. We also leverage skilled experts, consultants, contract research organizations, or CROs, and contractors to assist in managing our research and development operations under the leadership and direction of our management.

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 the proceeds received from the sales of common and preferred stock as well as capital contributions from the Predecessor Company and the former parent company, Rhythm Holdings LLC, or the LLC entity. Since our initial public offering, or IPO, on October 10, 2017 through our October 18, 2019 public offering, we have raised aggregate gross proceeds of our common stock of approximately $484.5 million before deducting underwriting discounts, commissions and offering related transaction costs. 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 December 31, 2019 we had an accumulated deficit of $325.3 million. Our net losses were $140.7 million and $74.1 million, for the years ended December 31, 2019 and 2018, 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 and the manufacture of RM-853 for preclinical development;

- 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 December 31, 2019, our existing cash and cash equivalents and short-term investments were approximately $292.5 million. We expect that our existing cash and cash equivalents and short-term investments will enable us to fund our operating expenses through at least the end of 2021.

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 a corporate reorganization, 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 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.

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 unless and until we receive regulatory approval of setmelanotide. We cannot predict if, when, or to what extent we will generate revenues from the commercialization and sale of setmelanotide. Setmelanotide is currently our most advanced product candidate in clinical development, 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 and genetic sequencing efforts, and the clinical development of setmelanotide and RM-853, 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 and clinical study materials;
- the cost of genetic sequencing of potential patients in clinical studies; 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:

	December 31,	
Research and development summary	**2019**	**2018**
Research and development expense	$ 109,450	$ 50,337

We are unable to predict the duration and costs of the current or future clinical trials of our product candidates. 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 our product candidates 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 and RM-853 development programs progress. 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 not involved in R&D or commercial activities. 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	December 31, 2019	2018
Selling, general and administrative expense	$ 36,550	$ 28,080

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 Annual Report on Form 10-K, 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.

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, CMOs and consultants in connection with research and development activities.

We accrue our expenses related to CROs, CMOs and consultants based on our estimates of the services received and efforts expended pursuant to quotes and contracts with CROs, CMOs and consultants 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.

Stock-based compensation

We have a 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. As of December 31, 2019, we have reserved 5,933,764 shares of common stock under the 2017 Plan. 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 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. We have elected to account for forfeitures as they occur. Upon adopting Accounting Standards Update 2018-07, *Improvements to Nonemployee Share-Based Payment Accounting (Topic 718)* on July 1, 2018, we elected that unsettled equity-classified awards to nonemployees for which a measurement date has not been established be measured using the adoption date fair value.

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 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, 2019, 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, 2019, we had net operating loss carryforwards to reduce federal and state incomes taxes of approximately $268.0 million and $241.3 million, respectively. If not utilized, these carryforwards begin to expire in 2033. Of the federal net operating loss carryforwards at December 31, 2019, $194.8 million can be carried forward indefinitely. At December 31, 2019, we also had available research and development tax credits for federal and state income tax purposes of approximately $6.4 million and $1.9 million, respectively. Additionally, as of December 31, 2019, we had federal orphan drug credits related to qualifying research of $6.9 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 Internal Revenue Code of 1986, as amended, or 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 years ended December 31, 2019 and 2018.

The following table summarizes our results of operations for the years ended December 31, 2019 and 2018, together with the changes in those items in dollars and as a percentage:

	Year Ended December 31,		Change	
	2019	2018	$	%
	(in thousands)			
Statement of Operations Data:				
Operating Expenses:				
Research and development	$ 109,450	$ 50,337	$ 59,113	117 %
Selling, general, and administrative	36,550	28,080	8,470	30 %
Total operating expenses	146,000	78,417	67,583	86 %
Loss from operations	(146,000)	(78,417)	(67,583)	86 %
Other income, net	5,271	4,353	918	21 %
Net loss	$ (140,729)	$ (74,064)	$ (66,665)	90 %

Research and development expense. Research and development expense increased by $59.1 million to $109.5 million in 2019 from $50.3 million in 2018, an increase of 117%. The increase was primarily due to the following:

- an increase of $34.6 million related to our clinical trials associated with setmelanotide. We expanded the GO-ID genotyping study and the Phase 2 basket study with new trial sites for both studies, as well as ongoing enrollment in the Phase 3 study of setmelanotide in patients with BBS and Alström syndrome;

- an increase of $11.8 million related to translational research and genetic sequencing efforts designed to improve identification of patients with MC4R pathway deficiencies and pathway validation efforts;

- an increase of $6.8 million due to the hiring of additional full-time employees in order to support efforts for community building and education efforts for physicians, care providers and patients who are facing rare genetic disorders of obesity, as well as to support the growth of our research and development programs;

- an increase of $4.1 million primarily related to purchases of setmelanotide API and drug product for clinical trials, preparation for potential commercialization and pre-IND work for RM-853;

- an increase of $4.1 million in consulting and professional services associated with the creation of our EU Medical Science Liaison field force, our US Disease Education Liaison field force, various medical communication programs and ongoing support for our NDA filing; and

- the above increases were partially offset by a decrease of $4.4 million due to the non-cash expense related to the license acquired from Takeda for RM-853 in March 2018.

Selling, general and administrative expense. Selling, general and administrative expense increased by $8.5 million to $36.6 million in 2019 from $28.1 million in 2018, an increase of 30%. The increase was primarily due to the following:

- an increase of $6.9 million in employee related costs in connection with the hiring of additional full-time employees to support planned commercial activities, operations and the continued enhancements of finance, information technology, or IT, and human resource functions; and

- an increase of $1.2 million in various consulting and professional services related to IT support costs to support the growth in personnel and systems.

Liquidity and Capital Resources

As of December 31, 2019, our existing cash and cash equivalents and short-term investments were approximately $292.5 million.

Cash flows

The following table provides information regarding our cash flows for the years ended December 31, 2019 and 2018:

	Year Ended December 31,	
	2019	2018
	(in thousands)	
Net cash provided by (used in):		
Operating activities	$ (122,750)	$ (62,056)
Investing activities	(27,970)	(87,148)
Financing activities	163,474	164,686
Net increase in cash, cash equivalents and restricted cash	$ 12,754	15,482

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 $122.8 million for the year ended December 31, 2019, and consisted primarily of a net loss of $127.8 million adjusted for non-cash items, which consisted of non-cash stock-based compensation, depreciation and amortization and rent expense. The change in operating assets and liabilities reflected a total use of cash of approximately $6.4 million for an increase in prepaid expenses associated with our CROs and CMOs due to the timing of payments offset by an increase of $10.5 million in accounts payable and accrued expenses. We also received proceeds of $0.9 million from tenant improvement allowances related to our new office space.

Net cash used in operating activities was $62.1 million for the year ended December 31, 2018, and consisted primarily of a net loss of $62.7 million adjusted for non-cash items, which consisted of the non-cash research and development license expense for RM-853, stock-based compensation and depreciation and amortization.

Net cash used in investing activities

Net cash used in investing activities for the year ended December 31, 2019 relates to net purchases of short-term investments of $24.6 million and $3.4 million of cash used for tenant improvements and new furniture and fixtures related to our new office space.

Net cash used in investing activities for the year ended December 31, 2018 relates to the net purchases of short-term investments of $86.4 million and fixed asset additions of $0.7 million related to the implementation of our new enterprise resource planning system and costs related to the expansion of our office facilities following the amendment of our long-term lease.

Net cash provided by financing activities

Net cash provided by financing activities was $163.5 million for the year ended December 31, 2019, which represents the net proceeds of $161.4 million from our common stock offering in October 2019 and $2.1 million of cash proceeds from the exercise of stock options and the issuance of common stock from the ESPP.

Net cash provided by financing activities was $164.7 million for the year ended December 31, 2018, which represents the net proceeds of $162.9 million from our common stock offering in June 2018 and $1.8 million of cash proceeds from the exercise of stock options.

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 short-term investments, will enable us to fund our operating expenses through at least the end of 2021. 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 costs to commercialize setmelanotide, if approved, by building an internal sales force or entering into collaborations with third parties and providing support services for patients;
- 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 following regulatory approval, 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. From August 2015 through August 2017, we raised aggregate gross proceeds of $81.0 million through our issuance of series A preferred stock. Since our IPO, in October 2017, through the October 2019 public offering, we have raised aggregate gross proceeds of our common stock of approximately $484.5 million before deducting underwriting discounts, commissions and offering related transaction costs.

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.

Based on our current development plans as of December 31, 2019, potential payments due to third parties, during the next 12 months from the filing of this annual report on Form 10-K are estimated to be approximately $8.0 million, including $3.0 million in regulatory milestones and $5.0 million in commercial milestones, in connection with our license agreements. These milestones generally become due and payable upon achievement of such milestones or sales. When the achievement of these milestones or sales have not occurred, such contingencies are not recorded in our financial statements and are excluded from the table below.

In August 2018, we amended our existing Lease Agreement for our head office facility in Boston, Massachusetts. The new lease term commenced in May 2019 and has a term of six years with a five-year renewal option to extend the lease. The new lease includes approximately 13,600 square feet of office space.

Future minimum payments under the Lease Agreement, as amended, are as follows:

	Operating Lease
2020	$ 786
2021	802
2022	818
2023	834
2024	851
Thereafter	502
Total	$ 4,593

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.

JOBS Act

In April 2012, the Jumpstart our Business Startups Act of 2012, or 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.

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 EGC 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 securities during the prior three-year period.

Even after we no longer qualify as an emerging growth company, we may still qualify as a “smaller reporting company” if the market value of our common stock held by non-affiliates is below $250 million (or below $700 million if

our annual revenue is less than $100 million) as of June 30 in any given year, which would allow us to take advantage of certain scaled disclosure requirements.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

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.

Item 8. Financial Statements and Supplementary Data

See the consolidated financial statements filed as part of this Annual Report on Form 10-K as listed under Item 15 below.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosures

Not Applicable.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our principal executive officer and principal financial officer, has evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13a- 15(e) and 15d- 15(e) under the Securities Exchange Act of 1934, as amended, as of the end of the period covered by this Annual Report on Form 10-K. Based on such evaluation, our principal executive officer and principal financial officer have concluded that as of December 31, 2019, our disclosure controls and procedures were effective.

Management's Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act). Internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles and includes those policies and procedures that:

(i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of our assets;

(ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that our receipts and expenditures are being made only in accordance with authorizations of our management and directors; and

(iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on our financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls

may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2019. In making this assessment, it used the criteria established in *Internal Control—Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). Based on such assessment, our management has concluded that our internal control over financial reporting was effective, as of December 31, 2019.

Changes in Internal Control Over Financial Reporting

There were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) that occurred during the fourth quarter of 2019 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

None

PART III

Item 10. Directors, Executive Officers and Corporate Governance

The information required under this item is incorporated herein by reference to our definitive proxy statement pursuant to Regulation 14A, which proxy statement will be filed with the Securities and Exchange Commission not later than 120 days after the close of our fiscal year ended December 31, 2019.

We intend to disclose on our website any amendments to, or waivers from, our Code of Business Conduct and Ethics that are required to be disclosed pursuant to the rules of the SEC. Our website is not considered part of this report or any other filing that we make with the SEC.

Item 11. Executive Compensation

The information required under this item is incorporated herein by reference to our definitive proxy statement pursuant to Regulation 14A, which proxy statement will be filed with the Securities and Exchange commission not later than 120 days after the close of our fiscal year ended December 31, 2019.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required under this item is incorporated herein by reference to our definitive proxy statement pursuant to Regulation 14A, which proxy statement will be filed with the Securities and Exchange commission not later than 120 days after the close of our fiscal year ended December 31, 2019.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required under this item is incorporated herein by reference to our definitive proxy statement pursuant to Regulation 14A, which proxy statement will be filed with the Securities and Exchange commission not later than 120 days after the close of our fiscal year ended December 31, 2019.

Item 14. Principal Accountant Fees and Services

The information required under this item is incorporated herein by reference to our definitive proxy statement pursuant to Regulation 14A, which proxy statement will be filed with the Securities and Exchange commission not later than 120 days after the close of our fiscal year ended December 31, 2019.

PART IV

Item 15. Exhibits and Financial Statement Schedules

(a) 1. Consolidated Financial Statements.

For a list of the consolidated financial statements included herein, see Index on page F-1 of this report.

2. Financial Statement Schedules.

All required information is included in the financial statements or notes thereto.

3. List of Exhibits.

See the Exhibit Index in Item 15(b) below.

Item 16. 10-K Summary

None

Exhibit Index

Exhibit Number	Exhibit Description	Incorporated by Reference		
		Form	Date	Number
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
4.3	Form of Subordinated Indenture to be entered into between the registrant and a trustee acceptable to the registrant.	S-3	11/9/2018	4.3
4.4	Form of Senior Indenture to be entered into between the registrant and a trustee acceptable to the registrant.	S-3	11/9/2018	4.4
4.5*	Description of the Registrant's Securities registered pursuant to Section 12 of the Securities Exchange Act of 1934.			
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†	Rhythm Pharmaceuticals, Inc. 2017 Employee Stock Purchase Plan.	10-Q	11/14/2017	10.10
10.7	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
10.8	First Amendment to Lease, dated April 15, 2016.	10-K	3/8/2019	10.9
10.9	Second Amendment to Lease, dated August 6, 2018.	8-K	8/9/2018	10.1
10.10†	Offer Letter, dated September 13, 2017, by and between the Registrant and Keith M. Gottesdiener.	10-Q	8/8/2018	10.2
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.	10-Q	8/8/2018	10.3
10.13†	Offer Letter, dated September 13, 2017, by and between the Registrant and Nithya Desikan.	10-Q	8/8/2018	10.4
10.14†	Summary of Non-Employee Director Compensation Policy.	10-Q	5/14/2018	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	5/14/2018	10.1
10.17†	First Amendment to the 2017 Employee Stock Purchase Plan.	S-1	6/18/2018	10.17
10.18†*	Form of Restricted Stock Unit Award Agreement.			
10.19†	Separation Agreement and General Release, by and between the Registrant and Keith Gottesdiener, dated January 6, 2020.	8-K	1/8/2020	10.1
10.20†	Consulting Agreement, by and between the Registrant and Keith Gottesdiener, dated January 6, 2020.	8-K	1/8/2020	10.2
23.1*	Consent of Ernst & Young LLP, Independent Registered Public Accounting Firm.			
31.1*	Certification of the Chief Executive Officer, as required by Section 302 of the Sarbanes-Oxley Act of 2002 (18 U.S.C. 1350).			
31.2*	Certification of the Chief Financial Officer, as required by Section 302 of the Sarbanes-Oxley Act of 2002 (18 U.S.C. 1350).			
32.1**	Certification of the Chief Executive Officer, as required by Section 906 of the Sarbanes-Oxley Act of 2002 (18 U.S.C. 1350).			
32.2**	Certification of the Chief Financial Officer, as required by Section 906 of the Sarbanes-Oxley Act of 2002 (18 U.S.C. 1350).			
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.			

* Filed herewith.
** Furnished and not filed herewith.
† Indicates management contract or compensatory plan.
‡ Indicates confidential treatment has been requested with respect to specific portions of this exhibit. Omitted portions have been filed with the Securities and Exchange Commission pursuant to Rule 406 of the Securities Act.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

RHYTHM PHARMACEUTICALS, INC.

By: /s/ Keith M. Gottesdiener
Keith M. Gottesdiener
Chief Executive Officer

Pursuant to the requirements of the Securities Act of 1934, this report has been signed by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Name	Title	Date
/s/ Keith M. Gottesdiener Keith M. Gottesdiener	Chief Executive Officer and Director (Principal Executive Officer)	March 2, 2020
/s/ Hunter Smith Hunter Smith	Chief Financial Officer (Principal Financial and Accounting Officer)	March 2, 2020
/s/ Stuart Arbuckle Stuart Arbuckle	Director	March 2, 2020
/s/ Todd Foley Todd Foley	Director	March 2, 2020
/s/ Jennifer Good Jennifer Good	Director	March 2, 2020
/s/ Christophe R. Jean Christophe R. Jean	Director	March 2, 2020
/s/ Ed Mathers Ed Mathers	Director	March 2, 2020
/s/ David W. J. McGirr David W. J. McGirr	Director	March 2, 2020
/s/ David P. Meeker David P. Meeker	Director, Chairman of the Board	March 2, 2020

RHYTHM PHARMACEUTICALS, INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

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, 2019 and 2018, 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, 2019, 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, 2019 and 2018, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2019, in conformity with U.S. generally accepted accounting principles.

Adoption of New Accounting Standards

As discussed in Note 2, *Summary of Significant Accounting Policies*, to the consolidated financial statements, the Company changed its method of accounting for leases in 2019 due to the adoption of Accounting Standards Update (ASU) No. 2016-02, *Leases (Topic 842)*, as amended, effective January 1, 2019, using the modified retrospective method.

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 2, 2020

RHYTHM PHARMACEUTICALS, INC.

CONSOLIDATED BALANCE SHEETS

(in thousands, except share and per share data)

	December 31, 2019	December 31, 2018
Assets		
Current assets:		
Cash and cash equivalents	$ 62,294	$ 49,542
Short-term investments	230,165	202,519
Prepaid expenses and other current assets	9,945	6,628
Total current assets	302,404	258,689
Property and equipment, net	3,671	1,120
Right-of-use asset	2,045	—
Restricted cash	403	401
Total assets	$ 308,523	$ 260,210
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 10,415	$ 7,640
Accrued expenses and other current liabilities	13,530	5,942
Lease liability	472	—
Total current liabilities	24,417	13,582
Long-term liabilities:		
Lease liability	3,086	—
Deferred rent	—	372
Total liabilities	27,503	13,954
Commitments and contingencies (Note 5 and 9)		
Stockholders' equity:		
Preferred Stock, $0.001 par value: 10,000,000 shares authorized; no shares issued and outstanding at December 31, 2019 and 2018	—	—
Common stock, $0.001 par value: 120,000,000 shares authorized; 43,996,753 and 34,410,725 shares issued and outstanding December 31, 2019 and 2018, respectively	44	34
Additional paid-in capital	606,307	430,824
Accumulated deficit	(325,331)	(184,602)
Total stockholders' equity	281,020	246,256
Total liabilities and stockholders' equity	$ 308,523	$ 260,210

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, 2019	Year Ended December 31, 2018	Year Ended December 31, 2017
Operating expenses:			
Research and development	$ 109,450	$ 50,337	$ 22,894
Selling, general, and administrative	36,550	28,080	9,518
Total operating expenses	146,000	78,417	32,412
Loss from operations	(146,000)	(78,417)	(32,412)
Other income (expense):			
Revaluation of Series A Investor Instrument and Series A Investor Right/Obligation	—	—	(1,863)
Interest income, net	5,271	4,353	566
Total other income, net	5,271	4,353	(1,297)
Net loss	$ (140,729)	$ (74,064)	$ (33,709)
Net loss attributable to common stockholders	$ (140,729)	$ (74,064)	$ (37,582)
Net loss per share attributable to common stockholders, basic and diluted	$ (3.86)	$ (2.39)	$ (2.83)
Weighted-average common shares outstanding, basic and diluted	36,422,450	31,004,047	13,267,960
Other comprehensive loss:			
Net loss	$ (140,729)	$ (74,064)	$ (33,709)
Unrealized gain on marketable securities	144	—	—
Comprehensive loss	$ (140,585)	$ (74,064)	$ (33,709)

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
	Shares	Amount	Shares	Amount	Shares	Amount			
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
Adoption of new accounting standard	—	—	—	—	—	—	286	(286)	—
Stock compensation expense	—	—	—	—	—	—	6,390	—	6,390
Shares issued for license agreement	—	—	223,544	—	—	—	4,448	—	4,448
Issuance of common stock upon completion of public offering, net of offering costs	—	—	6,591,800	7	—	—	162,871	—	162,878
Issuance of common stock in connection with exercise of stock options	—	—	311,241	—	—	—	1,808	—	1,808
Change in unrealized gain on marketable securities	—	—	—	—	—	—	8	—	8
Net loss	—	—	—	—	—	—	—	(74,064)	(74,064)
Balance at December 31, 2018	—	—	34,410,725	34	—	—	430,824	(184,602)	246,256
Stock compensation expense	—	—	—	—	—	—	11,875	—	11,875
Issuance of common stock in connection with ESPP	—	—	25,871	—	—	—	558	—	558
Issuance of common stock in connection with exercise of stock options	—	—	235,833	1	—	—	1,563	—	1,564
Issuance of common stock upon completion of public offering, net of offering costs	—	—	9,324,324	9	—	—	161,343	—	161,352
Change in unrealized gain on marketable securities	—	—	—	—	—	—	144	—	144
Net loss	—	—	—	—	—	—	—	(140,729)	(140,729)
Balance at December 31, 2019	—	$ —	43,996,753	$ 44	—	$ —	$ 606,307	$ (325,331)	$ 281,020

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)

	Year ended December 31,		
	2019	2018	2017
Operating activities			
Net loss	$ (140,729)	$ (74,064)	$ (33,709)
Adjustments to reconcile net loss to cash used in operating activities:			
Non-cash research and development license expense	—	4,448	—
Stock-based compensation expense	11,875	6,390	2,278
Depreciation and amortization	834	442	223
Non-cash rent expense	203	61	(76)
Mark to market revaluation of series A investor instrument	—	—	1,863
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	(6,378)	(6,286)	(1,889)
Deferred issuance costs	—	—	9
Tenant improvement allowance	938	—	—
Due to related party	—	—	(105)
Accounts payable, accrued expenses and other current liabilities	10,507	6,953	1,946
Net cash used in operating activities	(122,750)	(62,056)	(29,460)
Investing activities			
Purchases of short-term investments	(295,825)	(248,592)	(126,917)
Maturities of short-term investments	271,240	162,166	17,006
Purchases of property and equipment	(3,385)	(722)	(133)
Net cash used in investing activities	(27,970)	(87,148)	(110,044)
Financing activities			
Net proceeds from issuance of common stock	161,352	162,878	125,658
Proceeds from the exercise of stock options	1,564	1,808	700
Proceeds from issuance of common stock from ESPP	558	—	—
Net proceeds from issuance of Series A Convertible Preferred Stock	—	—	40,842
Net cash provided by financing activities	163,474	164,686	167,200
Net increase in cash, cash equivalents and restricted cash	12,754	15,482	27,696
Cash, cash equivalents and restricted cash at beginning of year	49,943	34,461	6,765
Cash, cash equivalents and restricted cash at end of year	$ 62,697	$ 49,943	$ 34,461

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" or "We"), is a late-stage biopharmaceutical company focused on the development and commercialization of therapeutics for the treatment of rare genetic disorders which are characterized by severe, early-onset obesity and an unrelenting hunger or hyperphagia. The Company's lead product candidate is setmelanotide, a potent melanocortin-4 receptor, or MC4R, agonist 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 MC4R pathway deficiencies. MC4R 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.

The Company's development efforts are initially focused on obesity related to several single gene-related, or monogenic, MC4R pathway deficiencies: pro-opiomelanocortin, or POMC, deficiency obesity; leptin receptor, or LEPR, deficiency obesity; Bardet-Biedl syndrome, or BBS; Alström syndrome; POMC or LEPR heterozygous deficiency obesity; steroid receptor coactivator 1, or SRC1, deficiency obesity; SH2B adapter protein 1, or SH2B1, deficiency obesity; MC4R deficiency obesity and Smith-Magenis syndrome, as well as additional disorders as part of investigator-initiated protocols. Currently, there are no effective or approved treatments for these MC4R pathway-related disorders. We believe that the MC4R 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.

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.

The Company is subject to risks and uncertainties common to early-stage companies in the biotechnology industry, including but not limited to, risks associated with completing preclinical studies and clinical trials, receiving regulatory approvals for product candidates, development by competitors of new biopharmaceutical products, dependence on key personnel, protection of proprietary technology, compliance with government regulations and the ability to secure additional capital to fund operations. Product candidates currently under development will require significant additional research and development efforts, including preclinical and clinical testing and regulatory approval, prior to commercialization. These efforts require significant amounts of additional capital, adequate personnel and infrastructure and extensive compliance-reporting capabilities. Even if the Company's product development efforts are successful, it is uncertain when, if ever, the Company will realize revenue from product sales.

Corporate Reorganization

The Company is 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 its organization and a corporate reorganization, the Company was 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.

Liquidity

The Company has incurred operating losses and negative cash flows from operations since inception. As of December 31, 2019, the Company had an accumulated deficit of $325,331. The Company has primarily funded these

losses through the proceeds from the sales of common and preferred stock as well as capital contributions received from the Predecessor Company and the former parent company, Rhythm Holdings LLC, or the LLC entity. 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, pre-commercialization activities 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 December 31, 2019, the Company had $292,459 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 operations through at least the next twelve months from the filing of this Annual Report on Form 10-K with the SEC.

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").

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 research and development accrued expenses, stock-based compensation expense and the valuation allowance on the Company's deferred tax assets. Estimates are periodically reviewed in light of changes in circumstances, facts and experience. Changes in estimates are recorded in the period in which they become known. Actual results could differ materially from those estimates.

Principles of Consolidation

The consolidated financial statements include the accounts of Rhythm Pharmaceuticals, Inc. and its wholly-owned 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 considers its chief executive officer, or CEO, as its chief operating decision maker. The Company and the CEO view the Company's 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. 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.

Restricted Cash

Restricted cash consists of security deposits in the form of letter of credits placed in separate restricted bank accounts as required under the terms of the Company's lease arrangement for its corporate office in Boston, Massachusetts and the Company's corporate travel credit cards.

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. Prepaid expenses and other current assets consists of the following:

	December 31,	
	2019	2018
Prepaid research and development costs	$ 6,438	$ 5,288
Other current assets	3,507	1,340
Prepaid expenses and other current assets	$ 9,945	$ 6,628

Property and Equipment

Property and Equipment consists of the following:

	Useful Life	December 31, 2019	December 31, 2018
Leasehold improvements	*	$ 2,705	$ 1,103
Office equipment	5 years	70	70
Computers and software	3 years	411	411
Furniture, fixtures and equipment	5 years	1,237	345
		4,423	1,929
Less accumulated depreciation and amortization		(752)	(809)
Property and Equipment, net		$ 3,671	$ 1,120

* Shorter of asset life or lease term.

Depreciation and amortization expense for the years ended December 31, 2019, 2018 and 2017 was $834, $442 and $223, respectively.

Property and equipment are recorded at cost. Depreciation and amortization is calculated using the straight-line method over the estimated useful lives of the assets. Upon disposal, retirement or sale, the cost of assets disposed of and the related accumulated depreciation are removed from the accounts and any resulting gain or loss is included in the results of operations. Expenditures for repairs and maintenance that do not improve or extend the lives of the respective assets are charged to expense as incurred.

Fair Value Measurements

Fair value is the price that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. Financial assets and liabilities carried at fair value are classified and disclosed in one of the following three categories:

Level 1 — Quoted market prices in active markets for identical assets or liabilities.

Level 2 — Observable inputs other than Level 1 prices, such as quoted prices for similar assets or liabilities; quoted prices in markets that are not active; or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities.

Level 3 — Unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities.

The Company’s cash equivalents and marketable securities at December 31, 2019 and 2018 were carried at fair value, determined according to the fair value hierarchy. See Note 4 for further discussion.

The carrying amounts reflected in the consolidated balance sheets for accounts payable and accrued expenses approximate their fair values due to their short-term maturities at December 31, 2019 and 2018, respectively.

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, or 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, 2018 of $210 is included as a deduction to research and development expense in the consolidated statements of operations and comprehensive loss. No grant income was received during the years ended December 31, 2019 or 2017.

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. The value of goods and services received from contract research organizations, or CROs, or contract manufacturing organizations, or CMOs, 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. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the studies or clinical trials, including the phase or completion of events, invoices received and contracted costs. Significant judgments and estimates are made in determining the accrued balances at the end of any reporting period. Actual results could differ from the Company's estimates. The Company's historical accrual estimates have not been materially different from the actual costs.

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 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 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 its 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% 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, 2019, 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 more dilutive of the treasury-stock and if-converted methods. For purposes of the diluted net loss per share attributable to common stockholders calculation, 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 share equivalents, 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:

	Year Ended December 31,		
	2019	2018	2017
Stock options	3,428,497	2,616,530	1,832,639

Basic and diluted earnings per share is calculated as follows:

	Year Ended December 31,		
	2019	2018	2017
Numerator:			
Net loss	$ (140,729)	$ (74,064)	$ (33,709)
Cumulative dividends on convertible preferred shares	—	—	(3,873)
Loss attributable to common shares—basic and diluted	$ (140,729)	$ (74,064)	$ (37,582)
Denominator:			
Weighted-average number of common shares—basic and diluted	36,422,450	31,004,047	13,267,960
Loss per common share—basic and diluted	$ (3.86)	$ (2.39)	$ (2.83)

Comprehensive Income (Loss)

Comprehensive income (loss) represents the net change in shareholders’ equity during a period from sources other than transactions with shareholders. As reflected in the accompanying consolidated statements of operations and comprehensive loss, our comprehensive loss is comprised of net losses and unrealized gains and losses on marketable debt securities. These changes in equity are reflected net of tax.

Patent Costs

Costs to secure and defend patents are expensed as incurred and are classified as general and administrative expenses. Patent costs were $472, $637 and $180 for the years ended December 31, 2019, 2018 and 2017, 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 June 2016, the FASB issued ASU 2016-13, Financial Instruments-Credit Losses-Measurement of Credit Losses on Financial Instruments ("ASU 2016-13"). ASU 2016-13 requires the measurement and recognition of expected credit losses for financial assets held at amortized cost. ASU 2016-13 replaces the existing incurred loss impairment model with an expected loss methodology, which will result in more timely recognition of credit losses. ASU 2016-13 is effective for annual and interim reporting periods beginning after December 15, 2019. The Company does not anticipate this standard to have a significant impact on the consolidated financial statements.

In November 2016, the FASB issued ASU 2016-18, Statement of Cash Flows (Topic 230): Restricted Cash ("ASU 2016-18"). ASU 2016-18 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. The Company adopted this ASU on January 1, 2018 and has applied its content to statements of cash flows for the years ended December 31, 2019, 2018 and 2017 presented herein.

In June 2018, the FASB issued ASU 2018-07, Compensation-Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting ("ASU 2018-07"). ASU 2018-07 expands the scope of Topic 718 to include share-based payment transactions for acquiring goods and services from nonemployees. An entity should apply the requirements of Topic 718 to nonemployee awards except for certain exemptions specified in the amendment. This ASU is effective for fiscal years, and interim periods within those years, beginning after December 15, 2018, and early adoption is permitted. The Company has early adopted ASU 2018-07 in July 2018. The guidance has been adopted using the modified-retrospective approach, which requires that unsettled equity-classified awards for which a measurement date has not been established be measured using the adoption date fair value. The adoption of this ASU did not have a material impact on the Company's financial position or results of operations.

In August 2018, the FASB issued ASU 2018-15, Customer's Accounting for Implementation Costs in a Cloud Computing Arrangement That is a Service Contract ("ASU 2018-15"). ASU 2018-15 helps entities evaluate the accounting for fees paid by a customer in a cloud computing arrangement (hosting arrangement) by providing guidance for determining when the arrangement includes a software license. The amendments align the requirements for capitalizing implementation costs incurred in a hosting arrangement that is a service contract with the requirements for capitalizing

implementation costs incurred to develop or obtain internal-use software (and hosting arrangements that include an internal use software license). The accounting for the service element of a hosting arrangement that is a service contract is not affected by the amendments. This guidance will become effective in fiscal years beginning after December 15, 2019. Early adoption is permitted, including adoption in any interim period. The Company has early adopted ASU 2018-15 in the fourth quarter of 2018 and the adoption of this ASU did not have a material impact on the Company's financial position or results of operations.

Effective January 1, 2019 the Company adopted FASB ASU 2016-02, Leases (Topic 842) ("ASU 2016-02"). ASU 2016-02 requires lessees to recognize a right-of-use ("ROU") asset and lease liability for most lease arrangements. The new standard is effective for annual reporting periods beginning after December 15, 2018. The original guidance required application on a modified retrospective basis with the earliest period presented. In August 2018, the FASB issued ASU 2018-11, Targeted Improvements to ASC 842, which included an option to not restate comparative periods in transition and elect to use the effective date of ASC 842, as the date of initial application of transition, which the Company has elected. In addition, the Company elected the package of practical expedients permitted under the transition guidance within the new standard which allowed us to carry forward the historical lease classification. As a result of the adoption of ASC 842 on January 1, 2019, the Company recorded both an operating lease right-of-use asset of $3,265 and a lease liability of $3,636. Additional information and disclosures required by this new standard are contained in Note 5, Right Of Use Asset and Lease Liability.

In December 2019, the FASB issued ASU 2019-12, Income Taxes-Simplifying the Accounting for Income Taxes ("ASU 2019-12"). ASU 2019-12 eliminates certain exceptions related to the approach for intraperiod tax allocation, the methodology for calculating income taxes in an interim period and the recognition of deferred tax liabilities for outside basis differences. The new guidance also simplifies aspects of the accounting for franchise taxes and enacted changes in tax laws or rates and clarifies the accounting for transactions that result in a step-up in the tax basis of goodwill. The standard is effective for annual periods beginning after December 15, 2020 and interim periods within, with early adoption permitted. Adoption of the standard requires certain changes to be made prospectively, with some changes to be made retrospectively. We are currently assessing the impact of this standard on our financial condition and results of operations.

3. Accrued Expenses

Accrued expenses consisted of the following:

	December 31, 2019	December 31, 2018
Research and development costs	$ 8,059	$ 2,614
Professional fees	1,439	858
Payroll related	3,655	2,410
Other	377	60
Accrued expenses	$ 13,530	$ 5,942

4. Fair Value of Financial Assets and Liability

As of December 31, 2019 and 2018, the carrying amount of cash and cash equivalents and short-term investments was $292,459 and $252,061, respectively, which approximates fair value. Cash and cash equivalents 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 $53,014 and $37,019 as of December 31, 2019 and 2018, 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 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.

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 December 31, 2019 using:			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash Equivalents:				
Corporate Debt Securities and Commercial Paper	$ —	$ 8,885	$ —	$ 8,885
Money Market Funds	53,014	—	—	53,014
Marketable Securities:				
Corporate Debt Securities and Commercial Paper	—	230,165	—	230,165
Total	$ 53,014	$ 239,050	$ —	$ 292,064

	Fair value Measurements as of December 31, 2018 using:			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash Equivalents:				
Corporate Debt Securities and Commercial Paper	$ —	$ 5,976	$ —	$ 5,976
Money Market Funds	37,019	—	—	37,019
Marketable Securities:				
Corporate Debt Securities and Commercial Paper	—	202,519	—	202,519
Total	$ 37,019	$ 208,495	$ —	$ 245,514

Marketable Securities

The following tables summarize the Company's marketable securities:

	December 31, 2019			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Assets				
Corporate debt securities and commercial paper	$ 230,155	$ 54	$ (44)	$ 230,165
	$ 230,155	$ 54	$ (44)	$ 230,165

	December 31, 2018			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Assets				
Corporate debt securities and commercial paper (due within 1 year)	$ 202,653	$ 23	$ (157)	$ 202,519
	$ 202,653	$ 23	$ (157)	$ 202,519

2017 Series A Investor Instrument

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. The Company had classified its 2017 Series A Investor Instrument as a liability as it was 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 expected benefit was 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 was estimated as a weighted-average of IPO and remain private scenarios, and the future value was converted to a present value assuming a closing date of August 15, 2017 and a nominal, risk-free discount rate.

The Company used the Black-Scholes option-pricing model to value the 2017 Series A Investor Call Option. The fair value of the Series A Investor Instrument is determined to be the sum of the probability-weighted fair values of the 2017 Series A Investor Right/Obligation and the 2017 Investor Call Option.

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	1,863
Reclassification of liability upon August 2017 Second Tranche Closing	(2,191)
Fair value at December 31, 2017	$ —

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	—

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.

5. Right Of Use Asset and Lease Liability

The Company has a material operating lease for its head office facility and other immaterial operating leases for certain equipment. The Company's office lease has a remaining lease term of 5.5 years. The Company has measured the lease liability associated with the office lease using a discount rate of 10%. The Company estimated the incremental borrowing rate for the leased asset based on a range of comparable interest rates the Company would incur to borrow an amount equal to the lease payments on a collateralized basis over a similar term in a similar economic environment. As of December 31, 2019, the Company has not entered into any lease arrangements classified as a finance lease.

Under ASC 842, the Company determines, at the inception of the contract, whether the contract is or contains a lease based on whether the contract provides the Company the right to control the use of a physically distinct asset or substantially all of the capacity of an asset. Leases with an initial noncancelable term of twelve months or less that do not include an option to purchase the underlying asset that the Company is reasonably certain to exercise are classified as short-term leases. The Company has elected as an accounting policy to exclude from the consolidated balance sheets a ROU asset and lease liability for short-term leases.

Upon adoption of ASC 842, the Company elected the transition relief package, permitted within the standard, pursuant to which the Company did not reassess the classification of existing leases, whether any expired or existing contracts contain a lease, and whether existing leases have any initial direct costs. The Company also elected the practical

expedient of not separating lease components from non-lease components for all leases. There was no cumulative-effective adjustment to the opening balance of retained earnings. The Company reviews all material contracts for embedded leases to determine if they have a right-of-use asset.

The Company recognizes rent expense on a straight-line basis over the lease period. The depreciable life of assets and leasehold improvement are limited by the expected lease term, unless there is a transfer of title or purchase option reasonably certain of exercise.

As a result of the adoption of ASC 842 on January 1, 2019, the Company recorded both an operating lease right-of-use asset of $3,265 and a lease liability of $3,636. The standard did not materially impact the consolidated statement of cash flows and had no impact on the consolidated income statement.

The Company's office lease includes both lease and non-lease components. Non-lease components relate to real estate taxes, insurance, operating expenses and common area maintenance, which are usually billed at actual amounts incurred proportionate to the Company's rented square feet of the building. These non-lease components are expensed by the Company as they are incurred and are not included in the measurement of the lease liability.

The Company's corporate headquarters is located in Boston, Massachusetts. This facility houses the Company's research, clinical, regulatory, commercial and administrative personnel. In August 2018, the Company amended its existing lease agreement and the new lease term commenced May 2019 and has a term of six years with a five-year renewal option to extend the lease. As of January 1, 2019, the Company has not included the five-year renewal option to extend the lease in its measurement of the ROU asset or lease liability. Rent expense, or operating lease costs, for the years ended December 31, 2019, 2018 and 2017 were $629, $359 and $215, respectively.

Supplemental cash flow information related to the Company's lease for the year ended December 31, 2019, includes cash payments of $425 used in the measurement of its operating lease liability.

The following table presents the maturities of the Company's operating lease liability related to office space as of December 31, 2019, all of which is under a non-cancellable operating lease:

	Operating Lease
2020	$ 786
2021	802
2022	818
2023	834
2024	851
Thereafter	502
Total operating lease payments	4,593
Less: imputed interest	1,035
Total operating lease liability	$ 3,558

6. Preferred Stock and Common Stock

Preferred Stock

Upon the closing of the IPO in October 2017, the Series A convertible preferred stock automatically converted into shares of common stock on a 9.17-for-1 basis.

Common Stock

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 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 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 net proceeds of $125,658 after deducting underwriting discounts, commissions and 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 8 for further discussion.

On June 25, 2018 the Company completed its public offering of 6,591,800 shares of common stock at an offering price of $26.42 per share, which included the exercise in full by the underwriters of their option to purchase up to 859,800 additional shares of common stock. The Company received net proceeds of $162,878 after deducting underwriting discounts, commissions and offering expenses.

On October 18, 2019 the Company completed a public offering of 9,324,324 shares of common stock at an offering price of $18.50 per share, which included the exercise in full by the underwriters of their option to purchase up to 1,216,216 additional shares of common stock. The Company received net proceeds of $161,352 after deducting underwriting discounts, commissions and offering expenses.

As of December 31, 2019, an aggregate of 3,096,344 shares of common stock were reserved for future issuance under our stock plans, including outstanding stock options to purchase 2,505,267 shares of common stock and 591,077 shares available for future grant under our 2017 Employee Stock Purchase Plan.

7. Stock-based Compensation

2017 Equity Incentive Plan

The Company has a 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. As of December 31, 2019 the Company has reserved 5,933,764 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, 2017 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 preceding fiscal year. On January 1, 2020, 2019 and 2018, 1,759,870, 1,376,429 and 1,091,366 shares, respectively, were added to the 2017 Plan. Notwithstanding the foregoing, the 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 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. 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 and quarterly vesting beginning on the grant date.

During the years ended December 31, 2019, 2018 and 2017, the Company granted 1,445,200, 1,218,790, and 1,112,717 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 relating to outstanding stock options granted under the Company’s stock option plan during the year ended December 31, 2019, 2018 and 2017 was $17.19, $17.27 and $4.98, respectively. Total intrinsic value of stock options exercised during the years ended December 31, 2019, 2018 and 2017 was $3,844, $7,980 and $588, respectively.

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,		
	2019	2018	2017
Risk-free interest rate	2.40 %	2.73 %	1.97 %
Expected term (in years)	6.07	5.89	5.95
Expected volatility	66.03 %	62.21 %	66.18 %
Expected dividend yield	—	—	—

The Company early adopted ASU 2018-07 in July 2018. The guidance was adopted using the modified-retrospective approach, which requires that unsettled equity-classified awards for which a measurement date has not been

established be measured using the adoption date fair value. The adoption of this ASU did not have a material impact on the Company's financial position or results of operations.

Prior to the adoption of ASU 2018-07, options granted to non-employees used an expected term of 10 years, which is the contractual term of each option. All other assumptions used to calculate the grant date fair value are generally consistent with the assumptions used for options granted to employees.

A summary of the Company's common stock option activity for the year ended December 31, 2019 is as follows:

	Number of Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term	Aggregate Intrinsic Value
Outstanding as of December 31, 2018	2,616,530	$ 16.67	8.58	$ —
Granted	1,445,200	27.98	—	—
Exercised	(235,833)	6.63	—	3,844
Cancelled	(397,400)	24.85	—	—
Outstanding as of December 31, 2019	3,428,497	$ 21.17	7.94	$ 18,643
Options vested and expected to vest as of December 31, 2019	3,428,497	$ 21.17	7.94	$ 18,643
Options exercisable at December 31, 2019	1,446,311	$ 16.03	7.11	$ 13,872

The following table summarizes the classification of the Company's stock-based compensation expenses related to stock options, restricted stock units and the employee stock purchase plan recognized in the Company's consolidated statements of operations and comprehensive loss.

	Year Ended December 31,		
	2019	2018	2017
Research and development	$ 5,163	$ 2,793	$ 927
Selling, general, and administrative	6,712	3,597	1,351
Total	$ 11,875	$ 6,390	$ 2,278

Stock-based compensation expense by award type recognized during the years ended December 31, 2019, 2018 and 2017 was as follows:

	Year Ended December 31,		
	2019	2018	2017
Stock options	$ 11,667	$ 6,241	$ 2,084
Employees stock purchase plan	208	65	—
Restricted stock units	—	84	194
Total	$ 11,875	$ 6,390	$ 2,278

During 2019 and 2017, there were certain awards subject to modification accounting under ASC 718-20-35-3 through 35-4. Per terms of separation with a former employee, accelerated vesting and time to exercise vested options were granted for the former employee’s stock option awards. As a result, the Company recognized incremental expense for the stock option awards of $56 and $254, respectively.

As of December 31, 2019, the Company has unrecognized compensation cost of $27,885 related to non-vested employee, non-employee and director awards that is expected to be recognized over a weighted-average period of 2.48 years.

2017 Employee Stock Purchase Plan

The Company has a 2017 Employee Stock Purchase Plan, or the 2017 ESPP, which became effective in connection with the completion of the Company's IPO in October 2017. As of December 31, 2019, a total of 591,077 shares of common stock were reserved for issuance under this plan. In addition, the number of shares authorized under the 2017 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. On January 1, 2020 and 2019, 439,968 and 344,107 shares, respectively, were added to the 2017 ESPP. Notwithstanding the foregoing, the 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. During the year ended December 31, 2019, 25,871 shares were issued under this plan.

8. Significant Agreements

License Agreements

Pursuant to a license agreement with Ipsen Pharma, S.A.S., or Ipsen, the Company has 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 MC4R program or that otherwise were covered by the licensed patents. 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.

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. 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. The fees associated with these milestones were recorded as research and development expenses during the year ended December 31, 2017 when the milestones criteria were met in full.

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.*

9. Commitments and Contingencies

Legal Proceedings

The Company, from time to time, may be party to litigation arising in the ordinary course of business. The Company was not subject to any material legal proceedings during the years ended December 31, 2019, 2018 and 2017 and to the best of its knowledge, no material legal proceedings are currently pending or threatened.

Other

The Company is party to various agreements, principally relating to licensed technology, that require future payments relating to milestones that may be met in subsequent periods, or royalties on future sales of specified products. See Note 8 for discussion of these arrangements. Additionally, the Company is party to various contracts with CROs and CMOs that generally provide for termination on notice, with the exact amounts in the event of termination to be based on the timing of the termination and the terms of the agreement.

Based on the Company's current development plans as of December 31, 2019, potential payments due to third parties during the next 12 months from the filing of this Annual Report on Form 10-K are estimated be approximately $8,000, including $3,000 in regulatory milestones and $5,000 in commercial milestones, in connection with our license agreements. These milestones generally become due and payable upon achievement of such milestones or sales. When the achievement of these milestones or sales have not occurred, such contingencies are not recorded in the Company's consolidated financial statements.

10. Related-Party Transactions

Expenses paid directly to consultants and vendors considered to be related parties amounted to $2,489, $2,005, and $2,400 for the years ended December 31, 2019, 2018 and 2017, respectively. Outstanding payments due to these related parties as of December 31, 2019 and 2018 were $264 and $260, respectively and were included within accounts payable on the balance sheet.

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 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.

For the years ended December 31, 2019, 2018 and 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.

A reconciliation of the income tax benefit at the federal statutory tax rate to the Company's effective income tax rate is as follows:

	As of December 31,		
	2019	2018	2017
Statutory tax rate	21.00 %	21.00 %	34.00 %
State tax, net of federal benefit	6.75 %	6.90 %	4.08 %
Research and development credit	2.49 %	1.52 %	1.87 %
Orphan drug credit	1.85 %	1.95 %	2.29 %
Tax law change	— %	— %	(27.98)%
Stock compensation	(0.10)%	0.46 %	(1.84)%
Investor instrument revaluation	— %	— %	(1.88)%
Other	0.20 %	0.05 %	(0.07)%
Change in valuation allowance	(32.19)%	(31.88)%	(10.47)%
Effective tax rate	— %	— %	— %

The principal components of the Company's deferred tax assets and liabilities are as follows:

	As of December 31,	
	2019	2018
Deferred tax assets:		
Net operating loss carryforwards	$ 71,524	$ 35,776
Research and development credits	7,876	3,456
Orphan drug credit	6,889	4,286
Capitalized license fee	1,734	1,760
Stock-based compensation	3,628	1,517
Other	2,006	884
Total deferred tax assets	93,657	47,679
Valuation allowance	(92,943)	(47,679)
Net deferred tax assets	714	—
Deferred tax liabilities:		
Operating lease right-of-use asset and other	(714)	—
Total deferred tax liabilities	$ (714)	$ —

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, 2019 and 2018, 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 $45,264 in 2019 and $23,605 in 2018 primarily relates to the net loss incurred by the Company during each period.

As of December 31, 2019, the Company had federal and state net operating loss carryforwards of approximately $268,009 and $241,314, 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. Of the federal net operating loss carryforwards at December 31, 2019, $194,843 can be carried forward indefinitely.

As of December 31, 2019, the Company had federal and state research tax credits of approximately $6,357 and $1,922, respectively, which may be used to offset future tax liabilities. Additionally, as of 2019, the Company had a federal orphan drug credit related to qualifying research of $6,889. 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, 2019 and 2018. 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 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, 2019 and 2018, 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. 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. The Company has evaluated all subsequent events and determined that there are no material recognized or unrecognized subsequent events requiring disclosure, other than as disclosed below.

On January 6, 2020, the Company announced that Keith Gottesdiener, M.D., the Company’s Chief Executive Officer and President, intends to step down from his roles with the Company following submission of the Company’s NDA filing with the FDA. Dr. Gottesdiener is expected to remain in his roles until the earlier of (i) the planned NDA filing, (ii) the start date of a new Chief Executive Officer of the Company, and (iii) March 31, 2020 (the Termination Date). Dr. Gottesdiener will also step down as a director of the Company on such date. Thereafter, Dr. Gottesdiener is expected to serve as a consultant to the Company until December 31, 2020.

In connection with the above announcement, the Company and Dr. Gottesdiener entered into a separation agreement which entitles Dr. Gottesdiener to certain severance payments and benefits as set forth therein (the Separation Agreement). In accordance with the terms of the Separation Agreement, the Company will pay Dr. Gottesdiener a severance amount equal to $531, equal to 12 months of base salary, to be paid in installments in accordance with the Company's normal payroll practices following the Termination Date. Dr. Gottesdiener will also receive an additional monthly payment for 12 months after his Termination Date which he may use to cover a portion of certain healthcare expenses. In addition, Dr. Gottesdiener will provide consulting services to the Company, and will be paid $10 per month for up to 10 hours of services, subject to the terms and conditions of the consulting agreement through December 31, 2020.

In connection with the Separation Agreement, the Company modified certain equity awards held by Dr. Gottesdiener. The modification included the continuation of vesting of stock options through the end of the consulting agreement and an extension of the post-termination exercise period for vested options from 90 days to up to two years. In connection with this modification, the Company will record an incremental compensation charge of $2,968 during the three months ended March 31, 2020.

13. Selected Quarterly Financial Data (unaudited)

The following table contains selected quarterly financial information from 2019 and 2018. 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, 2019	June 30, 2019	September 30, 2019	December 31, 2019
Total revenue	$ —	$ —	$ —	$ —
Total operating expenses	30,520	44,149	37,107	34,224
Other income (expense), net:	1,546	1,353	1,104	1,268
Net loss	(28,974)	(42,796)	(36,003)	(32,956)
Net loss attributable to common stockholders	$ (28,974)	$ (42,796)	$ (36,003)	$ (32,956)
Net loss attributable to common stockholders per common share, basic and diluted	$ (0.84)	$ (1.24)	$ (1.04)	$ (0.78)

	Three months ended			
	March 31, 2018	June 30, 2018	September 30, 2018	December 31, 2018
Total revenue	$ —	$ —	$ —	$ —
Total operating expenses	17,001	15,021	19,244	27,151
Other income (expense), net:	542	609	1,558	1,644
Net loss	(16,459)	(14,412)	(17,686)	(25,507)
Net loss attributable to common stockholders	$ (16,459)	$ (14,412)	$ (17,686)	$ (25,507)
Net loss attributable to common stockholders per common share, basic and diluted	$ (0.60)	$ (0.52)	$ (0.52)	$ (0.74)

Exhibit 4.5

DESCRIPTION OF THE REGISTRANT'S SECURITIES REGISTERED PURSUANT TO SECTION 12 OF THE SECURITIES EXCHANGE ACT OF 1934

As of December 31, 2019, Rhythm Pharmaceuticals, Inc. ("we," "our," "us," or the "Company") had one class of securities registered under Section 12 of the Securities Exchange Act of 1934, as amended: common stock, par value $0.001 per share.

The following description of our capital stock is a summary, does not purport to be complete and is subject to, and qualified in its entirety by reference to, our amended and restated certificate of incorporation and amended and restated bylaws, copies of which are incorporated by reference as exhibits to our Annual Report on Form 10-K of which this Exhibit 4.5 is a part, and the terms and provisions of the Delaware General Corporation Law, or DGCL. For more complete information, you should carefully review our amended and restated certificate of incorporation, amended and restated bylaws and the DGCL.

DESCRIPTION OF CAPITAL STOCK

Authorized Capital Stock

Our authorized capital stock consists of 120,000,000 shares of common stock, par value $0.001 per share, and 10,000,000 shares of preferred stock, par value $0.001 per share.

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.

Authorized but Unissued Capital Stock

The DGCL does not require stockholder approval for any issuance of authorized shares. However, the listing requirements of the Nasdaq Global Market, which apply so long as our common stock remains listed on the Nasdaq Global Market, 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 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 December 31, 2019, the holders of approximately 7.9 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 of 1933, as amended, or 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).

RHYTHM PHARMACEUTICALS, INC.
2017 EQUITY INCENTIVE PLAN

Restricted Stock Unit Agreement

This Restricted Stock Unit Agreement (this "Agreement"), dated as of [●] (the "Date of Grant"), is between Rhythm Pharmaceuticals, Inc., a corporation organized under the laws of the State of Delaware (the "Company") and [●] (the "Participant"). Capitalized terms used in this Agreement without definition shall have the respective meaning ascribed to such capitalized terms in the Rhythm Pharmaceuticals, Inc. 2017 Equity Incentive Plan (as the same may be amended from time to time, the "Plan").

1. Grant of Restricted Stock Units. Subject to the terms and conditions set forth in this Agreement and in the Plan, the Company hereby grants the Participant [●] Restricted Stock Units, subject to the restrictions set forth below and in the Plan (the "Stock Units"). Each Stock Unit represents the right of the Participant to receive a share of common stock of the Company ("Stock"), an amount of cash based on the value of a share of Stock, or any combination of the foregoing, as determined by the Committee, if and when the specified conditions are met in Section 3 below, and on the applicable settlement date set forth in Section 5 below.

2. No Rights Prior to Settlement. Stock Units represent hypothetical shares of Stock, and not actual shares of Stock. No shares of Stock shall be issued to the Participant at the time the grant of the Stock Units is made, and the Participant shall not be, and shall not have any of the rights or privileges of, a stockholder of the Company with respect to any Stock Units. The Participant shall not have any interest in any fund or specific assets of the Company by reason of this award.

3. Vesting.

a) As of the date of this Agreement, all of the Stock Units shall be unvested and subject to a Risk of Forfeiture pursuant to Section 4 below.

b) Subject to the terms of this Section 3, the Stock Units shall vest ratably in a series of four (4) equal annual installments, with the first of such annual installments becoming vested on the first anniversary of the Date of Grant and an additional annual installment becoming vested on that day of each year thereafter until the Stock Units have become fully vested, provided that the Participant continues his or her employment or other association with the Company or one of its Affiliates from the Date of Grant until any such applicable vesting date. For purposes of this Agreement, the term "Vesting Date" shall mean a date on which any or all of the Stock Units vest in accordance with the provisions of this Section 3.

c) The vesting of the Stock Units shall be cumulative, but shall not exceed 100% of the Stock Units. If the foregoing schedule would produce fractional Stock Units, the number of Stock Units that vest shall be rounded down to the nearest whole Stock Unit and the

fractional Stock Units will be accumulated so that the resulting whole Stock Units will be included in the number of Stock Units that become vested on the last Vesting Date.

d) Except as otherwise provided in a written employment agreement or severance agreement entered into by and between the Participant and the Company or an Affiliate thereof, in the event of a Change of Control before all of the Stock Units vest in accordance with Section 3(a) above, the applicable provisions of the Plan shall apply to the Stock Units, and the Committee may take such actions as it deems appropriate pursuant to the Plan.

e) Those Stock Units that vest pursuant to this Section 3 or pursuant to any action taken by the Committee pursuant to the Plan shall become free from the Risk of Forfeiture pursuant to Section 4 below.

4. Termination of Stock Units. If the Participant ceases employment or other association with the Company and its Affiliates for any reason before all of the Stock Units vest, any unvested Stock Units shall automatically terminate and shall be forfeited as of the date of the Participant's termination of employment or other association. No settlement or payment shall be made with respect to any unvested Stock Units that terminate as described in this Section 4.

5. Settlement of Stock Units and Tax Withholding.

a) If a Stock Unit vests in accordance with the provisions of Section 3 above, then, subject to the provisions of this Section 5(a) and Sections 5(b), 5(c) and 12 below, the Company shall issue to the Participant one share of Stock for such vested Stock Unit, or an amount of cash based on the value of a share of Stock for each vested Stock Unit, or a combination of the foregoing, as determined by the Committee, subject to applicable tax withholding obligations, as soon as reasonably practicable after the Vesting Date applicable to such vested Stock Unit. Notwithstanding anything express or implied in the foregoing provisions of this Section 5(a) to the contrary, in no event shall settlement of a vested Stock Unit occur later than the fifteenth day of the third calendar month following the calendar year in which the Vesting Date applicable to such vested Stock Unit occurs, and in no event shall Participant be permitted, directly or indirectly, to designate the calendar year of payment.

b) All obligations of the Company under this Agreement shall be subject to the right of the Company as set forth in the Plan to collect applicable federal, state, local, foreign or other withholding taxes if, when, and to the extent required by law prior to the issuance of shares of Stock or payment in cash. The Company shall satisfy any applicable withholding requirement with respect to the issuance of shares of Stock from proceeds of a same day or next-day sale of a portion of the shares of Stock effected by the Company's designated broker; the Participant's acceptance of the Stock Units shall constitute the Participant's authorization to the broker to effect such sale. In the event payment is to be made in a form other than shares of Stock, then the Company shall collect from the Participant the applicable withholding taxes pursuant to such procedures as the Company deems appropriate under the circumstances.

c) The obligation of the Company to deliver Stock shall also be subject to the condition that if at any time the Board shall determine in its discretion that the listing, registration or qualification of any shares of Stock upon any securities exchange or under any state or federal

law, or the consent or approval of any governmental regulatory body is necessary or desirable as a condition of, or in connection with, the issuance of such shares, such shares may not be issued in whole or in part unless such listing, registration, qualification, consent or approval shall have been effected or obtained free of any conditions not acceptable to the Board. The issuance of shares of Stock, if any, to the Participant pursuant to this Agreement is subject to any applicable laws or regulations of the United States or of any state, municipality or other country having jurisdiction thereof.

6. No Stockholder Rights. Neither the Participant, nor any person entitled to receive Stock Units in the event of the Participant's death, shall have any of the rights and privileges of a stockholder with respect to shares of Stock, including voting or dividend rights, until such shares of Stock have been issued upon settlement of Stock Units. The Participant acknowledges that no election under Section 83(b) of the Code is available with respect to Stock Units.

7. Grant Subject to Plan Provisions. This grant is made pursuant to the Plan, the terms of which are incorporated herein by reference, and in all respects shall be interpreted in accordance with the Plan. The grant and settlement of the Stock Units are subject to the provisions of the Plan and to interpretations, regulations and determinations concerning the Plan established from time to time by the Committee in accordance with the provisions of the Plan, including, but not limited to, provisions pertaining to (a) rights and obligations with respect to withholding taxes, (b) the registration, qualification or listing of the shares of Stock, (c) changes in capitalization of the Company and (d) other requirements of applicable law. The Committee shall have the authority to interpret and construe the Stock Units pursuant to the terms of the Plan, and its decisions shall be conclusive as to any questions arising hereunder.

8. No Employment or Other Rights. The grant of the Stock Units shall not confer upon the Participant any right to be retained by or in the employ or service of the Company or any Affiliate and shall not interfere in any way with the right of the Company or any Affiliate to terminate the Participant's employment or other association with the Company and its Affiliates. The right of the Company and any Affiliate to terminate at will the Participant's employment or other association at any time for any reason is specifically reserved.

9. Assignment and Transfers. The Stock Units are not transferable, and shall not be sold, transferred, pledged, assigned, or otherwise alienated or hypothecated, other than by will or by the laws of descent and distribution. This Agreement may be assigned by the Company without the Participant's consent.

10. Governing Law; Counterparts. This Agreement shall be construed and enforced in accordance with the laws of the State of Delaware, without regard to the conflict of laws principles thereof. This Agreement may be executed in one or more counterparts all of which together shall constitute but one instrument. In making proof of this Agreement it shall not be necessary to produce or account for more than one such counterpart.

11. Notice. Any notice to the Company provided for in this instrument shall be addressed to the Company, at the Company's principal place of business, addressed to the attention of the Company's Treasurer, and any notice to the Participant shall be addressed to such Participant

at his or her residence address last filed with the Company. Any notice shall be delivered in accordance with Section 18 of the Plan.

12. Application of Section 409A of the Code. This Agreement is intended to be exempt from or otherwise comply with the provisions of Section 409A of the Code. Notwithstanding the foregoing, if any Stock Units constitute "deferred compensation" under Section 409A of the Code and such Stock Units become vested upon the Participant's termination of employment (or other association), settlement of such vested Stock Units shall be delayed for a period of six (6) months after the Participant's termination of employment (or other association) if the Participant is a "specified employee" as defined under Section 409A of the Code and if required pursuant to Section 409A of the Code. If settlement of any Stock Units is delayed in accordance with the foregoing provisions of this Section 12, such Stock Units shall be settled and paid within thirty (30) days after the date that is six (6) months following the Participant's termination of employment (or other association). To the extent subject to Section 409A of the Code, settlement of the Stock Units may only be made in a manner and upon an event permitted by Section 409A of the Code, and each settlement of the Stock Units shall be treated as a separate payment, and the right to a series of installment payments under the Stock Units shall be treated as a right to a series of separate payments. In no event shall the Participant, directly or indirectly, designate the calendar year of payment. The Company may change or modify the terms of this Agreement without the Participant's consent or signature if the Company determines, in its sole discretion, that such change or modification is necessary for purposes of compliance with or exemption from the requirements of Section 409A of the Code or any regulations or other guidance issued thereunder. Notwithstanding the previous sentence, the Company may also amend the Plan or this Agreement or revoke the Stock Units to the extent permitted by the Plan.

[The remainder of this page is intentionally left blank. Signature page to follow.]

In Witness Whereof, the parties have executed this Agreement as of the date first above written.

RHYTHM PHARMACEUTICALS, INC.	**FIRST_NAME LAST_NAME**
By: Signature	Signature of Participant
Title:	:

Participant's Address:

ADDRESS_LINE_1
ADDRESS_LINE_2
CITY, STATE ZIPCODE

[Signature Page to Rhythm Pharmaceuticals, Inc. Restricted Stock Unit Agreement]

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the following Registration Statements:

(1) Registration Statement (Form S-3 No. 333-228323) of Rhythm Pharmaceuticals, Inc.,

(2) Registration Statement (Form S-8 No. 333-229642) pertaining to the 2017 Equity Incentive Plan and the 2017 Employee Stock Purchase Plan of Rhythm Pharmaceuticals, Inc.,

(3) Registration Statement (Form S-8 No. 333-223647) pertaining to the 2017 Equity Incentive Plan of Rhythm Pharmaceuticals, Inc., and

(4) Registration Statement (Form S-8 No. 333-220925) pertaining to the 2017 Equity Incentive Plan and the 2017 Employee Stock Purchase Plan of Rhythm Pharmaceuticals, Inc.;

of our report dated March 2, 2020, with respect to the consolidated financial statements of Rhythm Pharmaceuticals, Inc. included in this Annual Report (Form 10-K) of Rhythm Pharmaceuticals, Inc. for the year ended December 31, 2019.

/s/ Ernst & Young LLP

Boston, Massachusetts
March 2, 2020

Exhibit 31.1

CERTIFICATION OF PRINCIPAL EXECUTIVE OFFICER
PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Keith M. Gottesdiener, certify that:

1. I have reviewed this annual report on Form 10-K of Rhythm Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 2, 2020

/s/ Keith M. Gottesdiener
Name: Keith M. Gottesdiener
Title: Chief Executive Officer, President and Director
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION OF PRINCIPAL FINANCIAL OFFICER
PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Hunter Smith, certify that:

1. I have reviewed this annual report on Form 10-K of Rhythm Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 2, 2020

/s/ Hunter Smith
Name: Hunter Smith
Title: Chief Financial Officer and Treasurer
(Principal Financial And Accounting Officer)

Exhibit 32.1

CERTIFICATION OF CHIEF EXECUTIVE OFFICER
PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

I, Keith M. Gottesdiener, certify pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to my knowledge, the Annual Report on Form 10-K of Rhythm Pharmaceuticals, Inc. for the fiscal year ended December 31, 2019 fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934 and the information contained in such Form 10-K fairly presents, in all material respects, the financial condition and results of operations of Rhythm Pharmaceuticals, Inc.

/s/ Keith M. Gottesdiener
Name: Keith M. Gottesdiener
Title: Chief Executive Officer, President and Director
(Principal Executive Officer)

March 2, 2020

Exhibit 32.2

CERTIFICATION OF CHIEF FINANCIAL OFFICER
PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

I, Hunter Smith, certify pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to my knowledge, the Annual Report on Form 10-K of Rhythm Pharmaceuticals, Inc. for the fiscal year ended December 31, 2019 fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934 and the information contained in such Form 10-K fairly presents, in all material respects, the financial condition and results of operations of Rhythm Pharmaceuticals Inc.

/s/ Hunter Smith
Name: Hunter Smith
Title: Chief Financial Officer and Director
(Principal Financial and Accounting Officer)

March 2, 2020