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Subject to Completion, Dated October 15, 2019

PRELIMINARY PROSPECTUS SUPPLEMENT
(To Prospectus dated November 9, 2018)

$150,000,000

RHYTHM PHARMACEUTICALS, INC.

Common Stock

We are offering $150,000,000 of shares of our common stock.

Our common stock is listed on the Nasdaq Global Market under the symbol "RYTM." On October 14, 2019, the last reported sale price for our common stock on the Nasdaq Global Market was $20.41 per share.

We are an "emerging growth company" under applicable federal securities laws and, as such, have elected to comply with certain reduced public company reporting requirements for this prospectus supplement and future filings. See "Prospectus Supplement Summary—Status as an Emerging Growth Company."

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the accuracy or adequacy of this prospectus supplement or the accompanying prospectus. Any representation to the contrary is a criminal offense.

Investing in our common stock involves risks. See "Risk Factors" beginning on page S-13 of this prospectus supplement.

	Per Share	***Total***
Public offering price	*$*	*$*
Underwriting discounts and commissions(1)	*$*	*$*
Proceeds to us, before expenses	*$*	*$*

(1) We have also agreed to reimburse the underwriters for certain of their expenses. See "Underwriters" beginning on page S-28 of this prospectus supplement for more information about these arrangements.

We have granted the underwriters the right to purchase up to an aggregate of $22,500,000 of additional shares of our common stock from us at the public offering price, less underwriting discounts and commissions. The underwriters may exercise this right at any time, in whole or in part, within 30 days following the date of this prospectus supplement.

The underwriters expect to deliver the shares of common stock to investors in book-entry form through the facilities of The Depository Trust Company on or about October , 2019.

MORGAN STANLEY *GOLDMAN SACHS & CO. LLC* *COWEN*

NEEDHAM & COMPANY

The date of this prospectus supplement is October , 2019.

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ABOUT THIS PROSPECTUS SUPPLEMENT

This document is in two parts. The first part is this prospectus supplement, which describes the terms of the offering of the securities offered hereby and also adds to and updates the information contained in the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus. The second part is the accompanying prospectus, which provides more general information, some of which may not apply to this offering and some of which may have been supplemented or superseded by information in this prospectus supplement or documents incorporated or deemed to be incorporated by reference into this prospectus supplement that we filed with the SEC subsequent to the date of the prospectus. To the extent that there is any conflict between the information contained in this prospectus supplement, on the one hand, and the information contained in the accompanying prospectus or any document incorporated by reference herein or therein, on the other hand, you should rely on the information in this prospectus supplement.

This prospectus supplement and the accompanying prospectus are part of a registration statement that we filed with the Securities and Exchange Commission, or SEC, utilizing a "shelf" registration process as a "well-known seasoned issuer" as defined in Rule 405 under the Securities Act of 1933, as amended, or the Securities Act. Under this shelf registration process, we may offer from time to time various securities, of which this offering of shares of our common stock is a part. Such registration statement also includes exhibits that provide more detail on the matters discussed in this prospectus supplement and the accompanying prospectus. You should read this prospectus supplement, the accompanying prospectus, including the information incorporated by reference, the exhibits filed with the SEC, and any free writing prospectus that we have authorized for use in connection with this offering, in their entirety before making an investment decision.

You should rely only on the information contained in this prospectus supplement, the accompanying prospectus or incorporated herein or therein by reference and in any free writing prospectus that we have authorized for use in connection with this offering. We have not, and the underwriters have not, authorized anyone to provide you with information that is different. We and the underwriters are offering to sell, and seeking offers to buy, the securities offered hereby only in jurisdictions where offers and sales are permitted. The information contained, or incorporated by reference, in this prospectus supplement and contained, or incorporated by reference, in the accompanying prospectus is accurate only as of the respective dates thereof, regardless of the time of delivery of those respective documents, or of any sale of our shares of common stock. It is important for you to read and consider all information contained in this prospectus supplement and the accompanying prospectus, including the documents we have referred you to in the sections titled "Where You Can Find More Information" and "Incorporation of Certain Information by Reference" below.

The industry and market data contained or incorporated by reference into this prospectus supplement are based on independent industry publications, reports by market research firms or other published independent sources. Although we believe these sources are reliable, we have not independently verified the information and cannot guarantee its accuracy and completeness, as industry and market data are subject to change and cannot always be verified with complete certainty due to limits on the availability and reliability of raw data, the voluntary nature of the data gathering process and other limitations and uncertainties inherent in any statistical survey of market shares. Although we are not aware of any misstatements regarding the market and industry data presented or incorporated by reference into this prospectus supplement, these estimates involve risks and uncertainties and are subject to change based on various factors including those discussed in the section titled "Risk Factors." Accordingly, investors should not place undue reliance on this information.

The representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference in this prospectus supplement or the accompanying prospectus were made solely for the benefit of the parties to such agreement, including, in some cases, for

the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our business.

Unless otherwise indicated, all references to "us," "our," "RYTM," "we," the "Company" and similar designations refer to Rhythm Pharmaceuticals, Inc. or our predecessor company, as the context may require. Our principal executive offices are located at 222 Berkeley Street, Boston, MA 02116.

CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, including the information incorporated by reference into our prospectus or this prospectus supplement, contains, and any other prospectus supplement may contain "forward-looking statements" within the meaning of Section 27A of the Securities Act and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. You can identify these forward-looking statements by the use of words such as "outlook," "believes," "expects," "potential," "continues," "may," "will," "should," "seeks," "approximately," "predicts," "intends," "plans," "estimates," "anticipates" or the negative version of these words or other comparable words. These statements relate to future events or to our future operating or financial performance and involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements. We believe these factors include:

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

- our expectations regarding the period during which we qualify as an emerging growth company under the JOBS Act; and
- our use of the proceeds from this offering.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important cautionary statements in our prospectus or this prospectus supplement or in the documents incorporated by reference in our prospectus and this prospectus supplement, particularly in the "Risk Factors" section, that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. For a summary of such factors, please refer to the section entitled "Risk Factors" in our prospectus and this prospectus supplement, as updated and supplemented by the discussion of risks and uncertainties under "Risk Factors" contained in any further supplements to our prospectus and in our most recent annual report on Form 10-K, as revised or supplemented by our subsequent quarterly reports on Form 10-Q or our current reports on Form 8-K, as well as any amendments thereto, as filed with the SEC and which are incorporated herein by reference. The information contained in this document is believed to be current as of the date of this document. We do not intend to update any of the forward-looking statements after the date of this document to conform these statements to actual results or to changes in our expectations, except as required by law.

In light of these assumptions, risks and uncertainties, the results and events discussed in the forward-looking statements contained in our prospectus or this prospectus supplement or in any document incorporated herein by reference might not occur. Investors are cautioned not to place undue reliance on the forward-looking statements, which speak only as of the date of this prospectus supplement or the date of the document incorporated by reference in this prospectus supplement. We are not under any obligation, and we expressly disclaim any obligation, to update or alter any forward-looking statements, whether as a result of new information, future events or otherwise. All subsequent forward-looking statements attributable to us or to any person acting on our behalf are expressly qualified in their entirety by the cautionary statements contained or referred to in this section.

PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights certain information about us, this offering and selected information contained elsewhere in or incorporated by reference into this prospectus supplement or the accompanying prospectus. This summary is not complete and does not contain all of the information that you should consider before deciding whether to invest in our securities. For a more complete understanding of our company and this offering, we encourage you to read and consider carefully the more detailed information in this prospectus supplement and the accompanying prospectus, including the information under the heading "Risk Factors" in this prospectus supplement beginning on page S-13, in the accompanying prospectus beginning on page 4, and in our most recent Annual Report on Form 10-K, Quarterly Reports on Form 10-Q and the information incorporated by reference in this prospectus supplement and the accompanying prospectus.

Our Company

We are a biopharmaceutical company focused on the development and commercialization of therapeutics for the treatment of rare genetic disorders that result in severe, life-threatening metabolic disorders. Our lead peptide product candidate is setmelanotide, a potent, first-in-class 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 a group of single gene-related, or monogenic, MC4R pathway deficiencies: pro-opiomelanocortin, or POMC, deficiency obesity; leptin receptor, or LEPR, deficiency obesity; Bardet-Biedl syndrome; Alström syndrome; MC4R pathway heterozygous deficiency obesity; POMC epigenetic disorders; steroid receptor coactivator 1, or SRC1, deficiency obesity; SH2B adapter protein 1, or SH2B1, deficiency obesity; MC4R deficiency obesity; and Smith-Magenis syndrome. 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 have 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 Bardet-Biedl syndrome and Alström syndrome. In all four of these 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, Bardet-Biedl syndrome and Alström syndrome. We plan to complete our NDA submission for POMC deficiency obesity and LEPR deficiency obesity in the fourth quarter of 2019 or the first quarter of 2020.

We have demonstrated proof of concept in our Phase 2 clinical trial in Bardet-Biedl syndrome 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 expect to complete enrollment by the end of 2019 and report topline data in 2020. 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 400 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, ten are engaged in pre-commercialization activities and 14 are engaged in support administration, including business development and finance. In the near-term, we expect to expand our clinical, commercial and finance personnel, in particular, and will incur increased expenses as a result.

Recent Developments

Positive Topline Results from Pivotal Phase 3 Clinical Trials Evaluating Setmelanotide in POMC and LEPR Deficiency Obesities

We recently announced positive topline results from two pivotal, Phase 3 clinical trials evaluating setmelanotide for the treatment of POMC and LEPR deficiency obesities. 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 percent 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 percent ($p<0.0001$), and the mean reduction from baseline in most hunger rating for POMC deficiency obesity patients was –27.8 percent ($p=0.0005$). In addition, 50 percent of the POMC deficiency obesity patients in the trial met or exceeded a 25 percent 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.

Summary of Efficacy Endpoints	POMC
Primary: Proportion of Participants Achieving at Least 10% Change in Body Weight[i]	80% ($p<0.0001$)
Key Secondary: Mean Percent Reduction from Baseline in Body Weight[ii]	–25.4% 90% CI: –28.80, –21.98 ($p<0.0001$)
Key Secondary: Mean Percent Reduction from Baseline in Most Hunger Rating[ii]	–27.8% 90% CI: –40.58, –14.96 ($p=0.0005$)
Key Secondary: Proportion of Participants with 25% Reduction in Hunger[iii]	50% ($p=0.0004$)

Five of 11 patients with LEPR deficiency obesity achieved the primary endpoint of greater than 10 percent weight loss over one year ($p=0.0001$). The mean reduction from baseline in body weight for LEPR deficiency obesity patients was –12.5 percent ($p<0.0001$), and the mean reduction from baseline in

most hunger rating for LEPR deficiency obesity patients was –41.9 percent (p<0.0001). In addition, 72.7 percent of the LEPR deficiency obesity patients in the trial met or exceeded a 25 percent 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.

Summary of Efficacy Endpoints	LEPR
Primary: Proportion of Participants Achieving at Least 10% Change in Body Weight[i]	45.5% (p=0.0001)
Key Secondary: Mean Percent Reduction from Baseline in Body Weight[ii]	–12.5% 90% CI: –16.10, –8.83 (p<0.0001)
Key Secondary: Mean Percent Reduction from Baseline in Most Hunger Rating[ii]	–41.9% 90% CI: –54.76, –29.09 (p<0.0001)
Key Secondary: Proportion of Participants with 25% Reduction in Hunger[iii]	72.7% (p<0.0001)

In addition, the study design included a four-week placebo withdrawal period to further illustrate the effect of treatment with setmelanotide. Upon entry into the placebo period, participants almost immediately gained weight and experienced an increase in hunger, reversing their 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.

Consistent with prior clinical experience, setmelanotide was generally well-tolerated in both trials:

- Treatment-emergent related adverse events, or AEs, included injection site reactions, nausea and vomiting, and increased hyperpigmentation (darkening of the skin); these were consistent with prior clinical trials of setmelanotide.
- There were no reports of cardiovascular AEs related to setmelanotide.
- One LEPR study patient withdrew before the end of titration due to AE of mild hypereosinophilia.
- There were no serious adverse events, or SAEs, related to treatment with setmelanotide.
- 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 believe we are on track to complete submission of a rolling NDA to the FDA that will cover both POMC and LEPR deficiency obesities in the fourth quarter of 2019 or the first quarter of 2020. We also

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i Exact binomial test assessing whether proportion of responders after one year of treatment would be greater than a conservative comparator of 5 percent of patients achieving up to 10 percent body weight loss over one year without setmelanotide.

ii Endpoint analyzed on evaluable population, which includes participants who are at least 12 years of age who also achieved weight loss threshold (5kg or 5 percent if <100 kg) after 12 weeks.

iii Score is based on 0-10 Likert scale from question, "In the last 24 hours, how hungry did you feel when you were the most hungry?" for patients at least 12 years of age.

intend to request priority review of the application, which, if granted, could result in a six-month post-filing review process. Additionally, we expect to submit a Marketing Authorization Application, or MAA, with the European Medicines Agency, or EMA, which will cover both POMC and LEPR deficiency obesities.

We anticipate sharing the full data from these Phase 3 clinical trials in POMC and LEPR deficiency obesities in forthcoming publications and at presentations at upcoming medical meetings.

About Pivotal Phase 3 Trials in POMC and LEPR Deficiency Obesities

Our Phase 3 pivotal trials were designed in consultation with the FDA under Breakthrough Therapy status. Both trials are multicenter, open-label, single-arm trials that evaluated the efficacy and safety of setmelanotide for approximately one year in participants with either POMC or LEPR deficiency obesity who were 6 years of age and older.

Following screening and dose titration, participants received 12 weeks of therapeutic dose. There was also an eight-week blinded, drug withdrawal phase incorporated to further illustrate the effect of the drug. Lastly, participants received 32 weeks of therapeutic dose to complete approximately one year of treatment, before becoming eligible for the extension portion of the trial.

The primary endpoint in both studies assessed the percentage of participants who reached at least 10 percent weight loss as compared to historical controls in this population using an exact binomial comparison. Based on natural history data, it was expected that no participant would be a responder over the course of a year. To be conservative, a comparator of 5 percent of patients who could have lost 10 percent weight or more without treatment was used.

The first two key secondary endpoints were the mean percent reduction from baseline of body weight and most hunger rating. The third key secondary endpoint was a hunger score responder analysis comparing the proportion of patients who achieved at least a 25 percent reduction in hunger score.

In each study, all patients were included in the evaluation for the primary endpoint, the weight responder analysis. All patients were also included for the hunger responder analysis. For the other two key secondary endpoints, mean percent reductions in weight and hunger, participants were included in the evaluation if by week 12 they achieved 5 kg of weight loss.[iv] Nine POMC and seven LEPR patients were included in these groups.

We expect to continue to enroll supplemental patients in both the POMC and LEPR deficiency obesities Phase 3 trials, primarily focusing on pediatric patients between 6-11 years of age.

Orphan Drug Designation granted by FDA and Positive Opinion by the European Medicines Agency on Orphan Drug Designation for Setmelanotide for the Treatment of Bardet-Biedl Syndrome

We recently reported that the FDA granted orphan drug designation for setmelanotide for the treatment of Bardet-Biedl syndrome. 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. Accordingly, this designation may provide us with an extended exclusivity term in the United States. However, the orphan drug exclusivity does not prevent competitors from developing or marketing different drugs for Bardet-Biedl syndrome.

Also, on August 21, 2019, the European Commission adopted a decision designating setmelanotide as an orphan medicinal product for the treatment of patients with Bardet-Biedl syndrome. The orphan medicinal product designation by the European Commission is granted to medicines being developed for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition that affects

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[iv] Or 5 percent weight loss if their baseline weight was less than 100 kg.

fewer than five in 10,000 people in the European Union, or EU. This designation could allow for a number of incentives, including protocol assistance, access to the centralized authorization procedure, reduced regulatory fees, and a 10-year period of market exclusivity in the EU after product approval.

Expansion of Phase 2 Basket Study and Update on Genetic Sequencing Efforts and Phase 2 Clinical Trial

In September 2019, we announced that we added four new MC4R pathway-driven indications to our Phase 2 Basket Study. These indications were SRC1 deficiency obesity, SH2B1 deficiency obesity, MC4R deficiency obesity, and Smith-Magenis syndrome.

In addition, we also provided an update on our genetic sequencing efforts, which, as of June 2019, included samples from 13,567 individuals with severe obesity. Those samples 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.

Additionally, the results identified samples from 29 patients with POMC or LEPR deficiency obesity, which supports that these conditions are ultra-rare, even among the portion of the population with severe, early-onset obesity. These results are also consistent with our clinical epidemiology estimates of between 100 and 500 POMC deficiency obesity patients and between 500 and 2,000 LEPR deficiency obesity patients living in the United States. Furthermore, we believe the sequencing yield in this cohort supports our prior estimates of greater than 20,000 people living with high-impact heterozygous obesity of the POMC, PCSK1, or LEPR genes living in the United States.

For the genetically defined MC4R pathway indications that we have recently added to our Phase 2 Basket Study, we applied well-established functional and/or computational filtering processes to our genetic sequencing results. Based on these analyses, we estimate U.S. prevalence of greater than 23,000 for SRC1 deficiency obesity, greater than 24,000 for SH2B1 deficiency obesity, and greater than 10,000 for MC4R deficiency obesity.

In addition, we estimate that there are more than 2,400 people living with severe obesity and Smith-Magenis syndrome in the United States.

Also in September 2019, we provided an update on data from our Phase 2 clinical trial in patients with Bardet-Biedl syndrome and Alström syndrome. As previously disclosed in January 2019, six of nine enrolled patients with Bardet-Biedl syndrome showed weight loss of greater than 10 percent on setmelanotide treatment. As of August 2019, each of the six patients with Bardet-Biedl syndrome either continued to maintain, or increased, their weight loss following approximately two years of treatment, with a mean weight reduction of 22 percent. Additionally, five of six patients continued to show a substantial decrease in hunger. Three patients have discontinued treatment.

In patients with Alström syndrome, the three patients on treatment as of November 2018 have continued on treatment. One of the three patients has demonstrated 20 percent weight loss and a 25 percent reduction in hunger score at greater than one year. One patient has not lost weight but demonstrated a 38 percent decrease in hunger and improved diabetes control at greater than one year, and a third patient achieved six percent weight loss without a change in hunger. All three patients plan to continue setmelanotide therapy in the long-term extension trial.

Financial Update

Our financial statements for the quarter ended September 30, 2019 will not be available until after this offering is completed and consequently will not be available to you prior to investing in this offering. Based upon preliminary estimates and information available to us as of the date of this prospectus supplement, we expect to report that we had approximately $162.4 million of cash, cash equivalents and short-term investments as of September 30, 2019. We have not yet completed our quarter-end financial close process for the quarter ended September 30, 2019. This estimate of our cash, cash equivalents and short-term

investments as of September 30, 2019 is preliminary and is subject to change upon completion of our financial statement closing procedures. There can be no assurance that our final cash position as of September 30, 2019 will not differ from these estimates, including as a result of review adjustments and any such changes could be material. Our independent registered public accountants have not audited, reviewed or performed any procedures with respect to such preliminary financial data and accordingly do not express an opinion or any other form of assurance with respect thereto. These results could change as a result of further review. Complete quarterly results will be included in our Quarterly Report on Form 10-Q for the quarter ended September 30, 2019.

Company Information

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. Our principal executive offices are located at 222 Berkeley Street, Boston, MA 02116, and our telephone number is (857) 264-4280. Our corporate website address is *www.rhythmtx.com*. Information contained on or accessible through our website is not a part of this prospectus supplement, and the inclusion of our website address in this prospectus supplement is an inactive textual reference only.

Implications of Being an Emerging Growth Company

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

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

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

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

We have elected to take advantage of certain of the reduced disclosure obligations in the registration statement of which this prospectus supplement forms a part and may elect to take advantage of other reduced reporting requirements in future filings. As a result, the information that we provide to our

stockholders may be different from the information that you might receive from other public reporting companies in which you hold equity interests.

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

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.

THE OFFERING

Common stock offered by us	$150,000,000 of shares of our common stock
Common stock to be outstanding after this offering	shares (or shares if the underwriters exercise their option to purchase additional shares in full)
Option to purchase additional common stock offered by us	Up to $22,500,000 of shares of our common stock
Use of Proceeds	We estimate that our net proceeds from this offering will be approximately $ million, or approximately $ million if the underwriters exercise their option to purchase additional shares in full, after deducting underwriting discounts and commissions and estimated offering expenses payable by us. We intend to use the net proceeds from this offering, together with our existing cash resources, as follows: • clinical development; • translational research & genotyping; • preparing regulatory submissions and preparing for commercialization of setmelanotide; and • working capital and general and administrative expenses.
Risk Factors	See "Risk Factors" beginning on page S-13 of this prospectus supplement and in the documents incorporated by reference in this prospectus supplement and the accompanying prospectus.
Nasdaq Global Market Symbol	"RYTM"

The number of shares of our common stock to be outstanding after this offering is based on 34,497,542 shares of our common stock outstanding as of June 30, 2019 and excludes:

- 80,579 shares of common stock issued upon the exercise of stock options after June 30, 2019 at a weighted average exercise price of $6.53 per share;
- 2,394,131 shares of common stock reserved for future issuance under our 2017 equity incentive plan, or the 2017 Plan, as of June 30, 2019;
- 604,843 shares of common stock reserved for future issuance under our 2017 employee stock purchase plan, as of June 30, 2019; and
- 3,700,754 shares of common stock issuable upon the exercise of stock options outstanding as of June 30, 2019 under our 2017 Plan at a weighted average exercise price of $20.85.

In this prospectus supplement, unless otherwise indicated, the number of shares of common stock outstanding as of June 30, 2019 and the other information based thereon assumes no exercise by the underwriters of their option to purchase up to $22,500,000 of additional shares of common stock and no exercise of the outstanding options described above.

RISK FACTORS

Before you make a decision to invest in our securities, you should consider carefully the risks described below, together with other information in this prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein, including those risks identified under "Item 1A. Risk Factors" in our Annual Report on Form 10-K for the year ended December 31, 2018, and our Quarterly Reports on Form 10-Q for the periods ended March 31, 2019 and June 30, 2019, which are incorporated by reference in this prospectus supplement and which may be amended, supplemented or superseded by other reports that we subsequently file with the SEC. If any of the following events actually occur, our business, operating results, prospects or financial condition could be materially and adversely affected. This could cause the trading price of our common stock to decline and you may lose all or part of your investment. The risks described below are not the only ones that we face. Additional risks not presently known to us or that we currently deem immaterial may also significantly impair our business operations and could result in a complete loss of your investment. Please also read carefully the section entitled "Special Note Regarding Forward-Looking Statements."

Risks Related to this Offering

Management will have broad discretion as to the use of the proceeds from this offering and may not use the proceeds effectively.

Because we have not designated the amount of net proceeds from this offering to be used for any particular purpose, our management will have broad discretion as to the application of the net proceeds from this offering and could use them for purposes other than those contemplated at the time of the offering. Our management may use the net proceeds for corporate purposes that may not improve our financial condition or market value.

You will experience immediate and substantial dilution in the book value per share of the shares of common stock you purchase in this offering and may experience further dilution in the future.

The public offering price of the common stock offered pursuant to this prospectus supplement is substantially higher than the net tangible book value per share of our common stock. Therefore, you will incur immediate and substantial dilution in the net tangible book value per share of common stock from the public offering price per share of $. See the section titled "Dilution" on page S-22 below for a more detailed discussion of the dilution investors in this offering will incur if they purchase our common stock in this offering. In addition, in the past, we issued options to acquire shares of our common stock. To the extent that outstanding options are ultimately exercised, you will sustain future dilution.

You may experience future dilution as a result of future equity offerings.

In order to raise additional capital, we may in the future offer additional shares of common stock or other securities convertible into or exchangeable for our shares of common stock at prices that may not be the same as the prices per share in this offering. We may sell shares or other securities in any other offering at a price per share that is less than the price per share paid by investors in this offering, and investors purchasing shares or other securities in the future could have rights superior to existing shareholders. The price per share at which we sell additional shares of common stock, or securities convertible or exchangeable into shares of common stock, in future transactions may be higher or lower than the prices per share paid by investors in this offering.

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be your sole source of gain.

We have never paid or declared any cash dividends on our capital stock. We currently intend to retain earnings, if any, to finance the growth and development of our business and we do not anticipate paying

any cash dividends in the foreseeable future. As a result, only appreciation of the price of our common stock will provide a return, if any, to our stockholders.

Sales of a substantial number of our common stock by our existing shareholders in the public market could cause our stock price to fall.

If our existing shareholders sell, or indicate an intention to sell, substantial amounts of our common stock in the public market, the trading price of our common stock could decline. In addition, a substantial number of shares of common stock are subject to outstanding options are or will become eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules. If these additional shares of common stock are sold, or if it is perceived that they will be sold, in the public market, the trading price of our common stock could decline.

We, our executive officers and directors and certain of our shareholders have agreed that, subject to certain exceptions, during the period ending 90 days after the date of this prospectus supplement, we and they will not offer, sell, contract to sell, pledge or otherwise dispose of, directly or indirectly, any of our common stock or securities convertible into or exchangeable or exercisable for any of our common stock, enter into a transaction that would have the same effect, or enter into any swap or other arrangement that transfers, in whole or in part, any of the economic consequences of ownership of our common stock, whether any of these transactions are to be settled by delivery of our common stock or other securities, in cash or otherwise, or publicly disclose the intention to make any offer, sale, pledge or disposition, or to enter into any transaction, swap, hedge or other arrangement, without, in each case, the prior written consent of the representatives of the underwriters, who may release any of the securities subject to these lock-up agreements at any time without notice. Exceptions to the lock-up restrictions are described in more detail in this prospectus supplement under the caption "Underwriters."

Risks Related to our Business

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

The reported results of our Phase 3 clinical trial for POMC and LEPR deficiency obesities that we have publicly disclosed, and that are discussed herein, consist of top-line data. Top-line 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. Top-line 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 top-line results of our Phase 3 trial 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 top-line data that we have reported related to our Phase 3 trial 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 top-line data from our Phase 3 clinical trial 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 trial 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 trial. 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 trial, 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.

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 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 Bardet-Biedl syndrome is approximately 1,500 to 2,500 patients in the United States based on:
  - published prevalence estimates of one in 100,000 in North America, which projects to approximately 3,250 people in the United States. We believe the majority of these patients are addressable patients; and
  - our belief that with wider availability of genetic testing expected for Bardet-Biedl syndrome and increased awareness of new treatments, the number of patients diagnosed with this disorder will increase.
- *Alström Syndrome.* Our addressable patient population estimate for Alström syndrome is approximately 500 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.
- *High Impact MC4R Pathway Heterozygous Patients.* Our addressable patient population estimate for High Impact MC4R Pathway Heterozygous, or High Impact Het, patients (the subset of MC4R pathway heterozygous patients with well-characterized, published, high-impact loss-of-function variants, 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 High-Impact Het patients 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 and 90% of patients with Smith-Magenis syndrome have 17p11.2 chromosomal deletion, 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 June 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. 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. 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 these rare disorders. 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.

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 intend to focus 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 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 may likely be necessary. *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 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 will require product labeling that limits use to only those patients who express the genetic variants identified by the device. Moreover, even if setmelanotide and 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 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.

USE OF PROCEEDS

We estimate that the net proceeds from this offering will be approximately $ million, or approximately $ million if the underwriters exercise their option to purchase additional shares of common stock in full, in each case after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

We currently intend to use the net proceeds for clinical development, translational research & genotyping, preparing regulatory submissions and preparing for commercialization of setmelanotide, working capital and general and administrative expenses. This expected use of our net proceeds from this offering represents our intentions based upon our current plans and business conditions. As of the date of this prospectus supplement, we cannot specify with certainty all of the particular uses for the net proceeds that we will have from the sale of the shares of common stock or the amounts that we will actually spend on the uses set forth above. The amount and timing of our actual expenditures will depend upon numerous factors, including the results of our research and development efforts, the timing and success of clinical studies, our ongoing clinical trials or clinical trials we may commence in the future and the timing of regulatory submissions. Accordingly, our management will have broad discretion in the application of the net proceeds, and we may use the proceeds for purposes that are not contemplated at the time of this offering.

Based on our current plans, we believe our cash and cash equivalents, together with the net proceeds from this offering and excluding net proceeds from any exercise of the underwriters' option to purchase additional shares of our common stock, will be sufficient to fund our operations into the fourth quarter of 2021.

Pending our use of the net proceeds we receive from this offering, we intend to invest such net proceeds in a variety of capital preservation investments, including short-term, investment grade, interest bearing instruments and U.S. government securities.

DIVIDEND POLICY

We have never paid cash dividends on our common stock and we do not anticipate paying cash dividends in the foreseeable future, but intend to retain our capital resources for reinvestment in our business. Any future determination to pay cash dividends on our common stock will be at the discretion of our Board of Directors and will be dependent upon our financial condition, results of operations, capital requirements and other factors as the Board of Directors deems relevant.

DILUTION

If you purchase shares of our common stock in this offering, your interest will be diluted immediately to the extent of the difference between the public offering price per share and the net tangible book value per share of our common stock immediately after this offering. We calculate net tangible book value per share by dividing our net tangible assets (tangible assets less total liabilities) by the number of shares of our common stock outstanding.

Our historical net tangible book value at June 30, 2019 was $181.5 million, or $5.26 per share. After giving effect to the sale of shares of common stock in this offering at an offering price of $ per share, and after deducting the underwriting discounts and commissions and estimated offering expenses payable by us, our adjusted net tangible book value as of June 30, 2019 would have been approximately $ million, or $ per share. This represents an immediate increase in the net tangible book value of $ per share of our common stock to our existing shareholders and an immediate dilution in net tangible book value of $ per share to new investors purchasing shares of common stock in this offering. The following table illustrates this per share dilution:

Public offering price per share		$
Net tangible book value per share as of June 30, 2019	$ 5.26	
Increase in net tangible book value per share attributable to this offering		
Net tangible book value per share as of June 30, 2019, as adjusted after giving effect to this offering		
Dilution per share to new investors purchasing shares in this offering		$

If the underwriters exercise in full their option to purchase additional shares of our common stock, our adjusted net tangible book value as of June 30, 2019 would have been $ million, or $ per share of common stock. This represents an immediate increase in net tangible book value per share of $ per share to existing shareholders, and an immediate dilution of $ per share to investors participating in this offering.

The above discussion and table is based on 34,497,542 shares of our common stock outstanding as of June 30, 2019 and excludes:

- 80,579 shares of common stock issued upon the exercise of stock options after June 30, 2019 at a weighted average exercise price of $6.53 per share;
- 2,394,131 shares of common stock reserved for future issuance under our 2017 Plan, as of June 30, 2019;
- 604,843 shares of common stock reserved for future issuance under our 2017 employee stock purchase plan, as of June 30, 2019; and
- 3,700,754 shares of common stock issuable upon the exercise of stock options outstanding as of June 30, 2019 under our 2017 Plan at a weighted average exercise price of $20.85.

To the extent that outstanding options are exercised, or other shares are issued, investors purchasing shares in this offering could experience further dilution. In addition, we may choose to raise additional capital due to market conditions or strategic considerations, even if we believe we have sufficient funds for our current or future operating plans. To the extent that additional capital is raised through the sale of equity or convertible debt securities, the issuance of those securities could result in further dilution to our shareholders.

MATERIAL UNITED STATES FEDERAL INCOME AND ESTATE TAX CONSEQUENCES TO NON-U.S. HOLDERS OF OUR COMMON STOCK

The following is a discussion of the material U.S. federal income and estate tax consequences of the acquisition, ownership, and disposition of our common stock to a non-U.S. holder that purchases shares of our common stock for cash in this offering. For purposes of this discussion, a "non-U.S. holder" means a beneficial owner (other than a partnership or other pass-through entity) of our common stock that is not, for U.S. federal income tax purposes:

- an individual who is a citizen or resident alien of the United States;
- a corporation or any other organization taxable as a corporation for U.S. federal income tax purposes, created or organized in the United States or under the laws of the United States or of any state thereof or the District of Columbia;
- an estate, the income of which is subject to U.S. federal income tax regardless of its source; or
- a trust if (i) the trust is subject to the primary supervision of a U.S. court and all substantial decisions of the trust are controlled by one or more U.S. persons or (ii) the trust has a valid election in effect under applicable U.S. Treasury regulations to be treated as a U.S. person.

This discussion does not address the tax treatment of partnerships (or other entities that are treated as partnerships, grantor trusts, or other pass-through entities for U.S. federal income tax purposes) or persons that hold their common stock through partnerships, grantor trusts or such other pass-through entities. The tax treatment of a partner in a partnership or a holder of an interest in another pass-through entity that will hold our common stock generally will depend upon the status of the partner or interest holder and the activities of the partner or interest holder and the partnership or other pass-through entity, as applicable. Such a partner or interest holder should consult his, her, or its own tax advisor regarding the tax consequences of the acquisition, ownership and disposition of our common stock through a partnership or other pass-through entity, as applicable.

This discussion is based upon the provisions of the Internal Revenue Code of 1986, as amended, or the Code, the U.S. Treasury regulations promulgated thereunder, judicial decisions, and published rulings, administrative procedures and other guidance of the Internal Revenue Service, which we refer to as the IRS, all as in effect as of the date hereof. These authorities are subject to change and to differing interpretations, possibly with retroactive effect, which could result in U.S. federal income or estate tax consequences different from those summarized below. No ruling has been or is expected to be sought from the IRS with respect to the matters summarized below, and there can be no assurance that the IRS will not take a contrary position regarding the U.S. federal income or estate tax consequences of the acquisition, ownership, or disposition of our common stock, or that any such contrary position would not be sustained by a court.

This discussion is not a complete analysis of all of the potential U.S. federal income and estate tax consequences relating to the acquisition, ownership, and disposition of our common stock by non-U.S. holders, nor does it address any U.S. federal gift tax or generation-skipping transfer tax consequences, any tax consequences arising under any state, local, or non-U.S. tax laws, the impact of any applicable tax treaty, any consequences under the Medicare contribution tax on net investment income, the alternative minimum tax, or any consequences under other U.S. federal tax laws. In addition, this discussion does not address tax consequences resulting from a non-U.S. holder's particular circumstances or to non-U.S. holders that may be subject to special tax rules, including, without limitation:

- non-U.S. governments, agencies or instrumentalities thereof, or entities they control;
- "controlled foreign corporations" and their shareholders;
- "passive foreign investment companies" and their shareholders;

- partnerships, grantor trusts or other entities that are treated as pass-through entities for U.S. federal income tax purposes, and their owners;
- corporations that accumulate earnings to avoid U.S. federal income tax;
- former citizens or former long-term residents of the United States;
- banks, insurance companies or other financial institutions;
- tax-exempt pension funds or other tax-exempt organizations;
- persons who acquired our common stock pursuant to the exercise of employee stock options or otherwise as compensation;
- tax-qualified retirement plans;
- traders, brokers or dealers in securities, commodities or currencies;
- persons who hold our common stock as a position in a hedging transaction, wash sale, "straddle," "conversion transaction" or other risk reduction transaction or synthetic security;
- persons who do not hold our common stock as a capital asset within the meaning of Section 1221 of the Code (generally, for investment purposes);
- persons subject to special tax accounting rules as a result of any item of gross income with respect to our common stock being taken into account in a financial statement;
- persons who own or have owned, or are deemed to own or to have owned, more than 5% of our common stock, by value or voting power, (except to the extent specifically set forth below); or
- persons deemed to sell our common stock under the constructive sale provisions of the Code.

Prospective investors should consult their tax advisors regarding the particular U.S. federal income, estate, gift, and generation-skipping transfer tax consequences to them of acquiring, owning and disposing of our common stock, as well as any tax consequences arising under any state, local or foreign tax laws and any other U.S. federal tax laws. Prospective investors should also consult their tax advisors regarding the potential impact of any applicable income or estate tax treaty between the United States and such prospective investor's country of residence and of the rules described below under the heading "Foreign Account Tax Compliance Act."

Distributions on Common Stock

As described in the section entitled "Dividend Policy," we currently intend to retain all available funds and any future earnings for use in the operation of our business and do not anticipate paying any dividends on our common stock in the foreseeable future. The disclosure in this section addresses the consequences should our board of directors, in the future, determine to make a distribution of cash or property with respect to our common stock (other than certain distributions of stock which may be made free of tax), or to effect a redemption that is treated for tax purposes as a distribution. Any such distribution will generally constitute a dividend for U.S. federal tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. To the extent such a distribution exceeds both our current and our accumulated earnings and profits, such excess will be allocated ratably among the shares of common stock with respect to which the distribution is made, will constitute a return of capital, and will first be applied against and reduce the non-U.S. holder's adjusted tax basis in those shares of common stock, but not below zero. Distributions in excess of our current and accumulated earnings and profits and in excess of a non-U.S. holder's adjusted tax basis in that non-U.S. holder's shares of common stock then will be treated as gain from the sale of that common stock, subject to the tax treatment described below under "Gain on Disposition of Common Stock." A non-U.S. holder's adjusted tax basis in a share of common stock is generally the purchase price of the share, reduced by the amount of any distributions constituting a return of capital with respect to that share.

Any dividend paid to a non-U.S. holder of our common stock generally will be subject to U.S. federal withholding tax at a rate of 30% of the gross amount of the dividend, or such lower rate as may be specified by an applicable income tax treaty between the United States and such non-U.S. holder's country of residence. If a non-U.S. holder is eligible for benefits under an income tax treaty and wishes to claim a reduced rate of withholding, the non-U.S. holder generally will be required to provide us or our paying agent with a properly completed IRS Form W-8BEN, Form W-8BEN-E, or other applicable form, certifying under penalties of perjury the non-U.S. holder's qualification for the reduced rate. This certification must be provided to us or our paying agent prior to the payment of the dividend and may be required to be updated periodically. Special certification requirements apply to non-U.S. holders that hold common stock through certain foreign intermediaries. Non-U.S. holders that do not timely provide the required certifications, but that qualify for a reduced treaty rate, may obtain a refund of any excess amounts withheld by timely filing an appropriate claim for refund with the IRS. If we are not able to determine whether or not a distribution will exceed current and accumulated earnings and profits at the time the distribution is made, we may withhold tax on the entire amount of any distribution at the same rate as we would withhold on a dividend. However, a non-U.S. holder may obtain a refund of amounts that we withhold to the extent attributable to the portion of the distribution in excess of our current and accumulated earnings and profits.

If a non-U.S. holder holds our common stock in connection with the conduct of a trade or business in the U.S., and dividends paid on the common stock are effectively connected with the non-U.S. holder's U.S. trade or business (and, if required by an applicable income tax treaty between the United States and such non-U.S. holder's country of residence, are attributable to a permanent establishment or fixed base maintained by the non-U.S. holder in the U.S., as defined under the applicable treaty), the non-U.S. holder will be exempt from U.S. federal withholding tax on the dividends. To claim the exemption, the non-U.S. holder must furnish a properly executed IRS Form W-8ECI (or other applicable form) prior to the payment of the dividends. Any dividends paid on our common stock that are effectively connected with a non-U.S. holder's U.S. trade or business (and satisfy any other applicable treaty requirements) generally will be subject to U.S. federal income tax on a net income basis at the regular graduated U.S. federal income tax rates generally applicable to U.S. persons (as defined in the Code). A non-U.S. holder that is treated as a corporation for U.S. federal income tax purposes also may be subject to an additional branch profits tax equal to 30% (or such lower rate as is specified by an applicable income tax treaty between the United States and such non-U.S. holder's country of residence) of a portion of its earnings and profits for the taxable year that are effectively connected with a U.S. trade or business, as adjusted for certain items.

Gain on Disposition of Common Stock

Subject to the discussion below regarding backup withholding, a non-U.S. holder generally will not be subject to U.S. federal income tax on any gain realized upon the sale, exchange, or other taxable disposition of our common stock unless:

- the gain is effectively connected with the non-U.S. holder's conduct of a U.S. trade or business (and, if required by an applicable income tax treaty between the United States and such non-U.S. holder's country of residence, the gain is attributable to a permanent establishment or fixed base maintained by the non-U.S. holder in the United States), in which case the non-U.S. holder will generally be required to pay tax on the gain derived from the sale, exchange, or other taxable disposition (net of certain deductions or credits) under regular graduated U.S. federal income tax rates generally applicable to U.S. persons, and in the case of a non-U.S. holder that is treated as a corporation for U.S. federal income tax purposes, such non-U.S. holder may be subject to a branch profits tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and such non-U.S. holder's country of residence;

- the non-U.S. holder is an individual who is present in the U.S. for a period or periods aggregating 183 days or more during the taxable year in which the sale, exchange, or other taxable disposition occurs and certain other conditions are met, in which case the non-U.S. holder will be subject to

U.S. federal income tax at a flat 30% rate (or such lower rate as is specified by an applicable income tax treaty between the United States and such non-U.S. holder's country of residence) on the net gain derived from the sale, exchange, or other taxable disposition, which gain may be offset by U.S. source capital losses (even though the non-U.S. holder is not considered a resident of the United States) provided that the non-U.S. holder has timely filed U.S. federal income tax returns reporting those losses; or

- our common stock is a "United States real property interest" by reason of our status as a "United States real property holding corporation," or USRPHC, for U.S. federal income tax purposes during the five-year period preceding such sale, exchange or other taxable disposition (or the non-U.S. holder's holding period, if shorter). Generally, a corporation is a USRPHC only if the fair market value of its U.S. real property interests equals or exceeds 50% of the sum of the fair market value of its worldwide real property interests plus its other assets used or held for use in a trade or business.

We believe we are not now and we do not anticipate becoming a USRPHC. However, there can be no assurance that we are not now a USRPHC or will not become one in the future. Even if we are or become a USRPHC, for so long as our common stock is "regularly traded," as defined by applicable U.S. Treasury regulations, on an established securities market, sales of our common stock generally will not be subject to tax for non-U.S. holders that have not held more than 5% of our common stock, actually or constructively, during the five-year period preceding such non-U.S. holder's sale, exchange or other taxable disposition of our common stock (or the non-U.S. holder's holding period, if shorter). If we are determined to be a USRPHC and the foregoing exception does not apply, then the non-U.S. holder generally will be taxed on its net gain derived from the disposition at the graduated U.S. federal income tax rates applicable to U.S. persons. No assurance can be provided that our common stock will be regularly traded on an established securities market for purposes of the rule described above.

U.S. Federal Estate Tax

Shares of our common stock that are owned or treated as owned at the time of death by an individual who is not a citizen or resident of the United States, as specifically defined for U.S. federal estate tax purposes, are considered U.S. situs assets and will be included in the individual's gross estate for U.S. federal estate tax purposes. Such shares, therefore, may be subject to U.S. federal estate tax, unless an applicable estate tax or other treaty between the United States and such individual's country of residence provides otherwise.

Information Reporting and Backup Withholding

Generally, we or certain financial middlemen must report annually to the IRS and to each non-U.S. holder the gross amount of dividends and other distributions on our common stock paid to the non-U.S. holder and the amount of tax withheld, if any, with respect to those distributions. Pursuant to applicable income tax treaties or other agreements, the IRS may make these reports available to tax authorities in the non-U.S. holder's country of residence or incorporation.

A non-U.S. holder may be subject to backup withholding with respect to dividends paid on shares of our common stock, unless, generally, the non-U.S. holder certifies under penalties of perjury (usually on IRS Form W-8BEN or W-8BEN-E) that the non-U.S. holder is not a U.S. person or otherwise establishes an exemption. Dividends that are paid to non-U.S. holders subject to the withholding of U.S. federal income tax, as described above under the heading "Distributions on Common Stock" generally will be exempt from U.S. backup withholding.

Additional rules relating to information reporting requirements and backup withholding with respect to payments of the proceeds from the disposition of shares of our common stock are as follows:

- If the proceeds are paid to or through the U.S. office of a broker, the proceeds generally will be subject to backup withholding and information reporting, unless the non-U.S. holder certifies under

penalties of perjury (usually on IRS Form W-8BEN or W-8BEN-E) that the non-U.S. holder is not a U.S. person and satisfies certain other requirements or otherwise establishes an exemption.

- If the proceeds are paid to or through a non-U.S. office of a broker that is not a U.S. person and is not a foreign person with certain specified U.S. connections, which we refer to below as a "U.S.-related person," information reporting and backup withholding generally will not apply.

- If the proceeds are paid to or through a non-U.S. office of a broker that is a U.S. person or a U.S.-related person, the proceeds generally will be subject to information reporting (but not to backup withholding), unless the non-U.S. holder certifies under penalties of perjury (usually on IRS Form W-8BEN or W-8BEN-E) that the non-U.S. holder is not a U.S. person. A "U.S.-related person" includes (i) an entity classified as a "controlled foreign corporation" for U.S. federal income tax purposes, (ii) a foreign person, 50% or more of whose gross income from certain periods is effectively connected with a U.S. trade or business, or (iii) a foreign partnership if at any time during its tax year (a) one or more of its partners are U.S. persons who, in the aggregate, hold more than 50% of the income or capital interests of the partnership or (b) the foreign partnership is engaged in a U.S. trade or business.

Backup withholding is not an additional tax. Any amounts withheld from a non-U.S. holder under the backup withholding rules may be allowed as a refund or a credit against the non-U.S. holder's U.S. federal income tax liability, if any, provided that the non-U.S. holder timely furnishes the required information to the IRS. Non-U.S. holders should consult their own tax advisors regarding the application of the information reporting and backup withholding rules to them.

Foreign Account Tax Compliance Act

Sections 1471 to 1474 of the Code (commonly referred to as the Foreign Account Tax Compliance Act, or FATCA) generally impose withholding tax on certain types of payments made to "foreign financial institutions" (as defined in the Code) and other non-U.S. entities unless those institutions and entities meet additional certification, information reporting and other requirements. FATCA generally imposes a 30% withholding tax on dividends on our common stock paid to a foreign financial institution unless the foreign financial institution enters into an agreement with the U.S. Treasury to, among other things, (i) undertake to identify accounts held by certain U.S. persons (including certain equity and debt holders of such institution) or by U.S.-owned foreign entities, (ii) annually report certain information about such accounts, and (iii) withhold 30% on payments to account holders whose actions prevent it from complying with these reporting and other requirements. In addition, subject to certain exceptions, FATCA imposes a 30% withholding tax on dividends on our common stock paid to a "non-financial foreign entity" (as defined in the Code) unless the entity certifies that it does not have any substantial U.S. owners (which generally include any U.S. persons who directly or indirectly own more than 10% of the entity) or furnishes identifying information regarding each such substantial U.S. owner or agrees to report that information to the IRS. Withholding under FATCA generally will not be reduced or limited by bilateral income tax treaties. However, intergovernmental agreements between the U.S. and other countries with respect to the implementation of FATCA and non-U.S. laws, regulations and other authorities enacted or issued with respect to those intergovernmental agreements may modify the FATCA requirements described above. Because we may not know the extent to which a distribution is a dividend for U.S. federal income tax purposes at the time it is made, for purposes of these withholding rules we or the applicable withholding agent may treat the entire distribution as a dividend. Non-U.S. holders should consult their own tax advisors regarding the possible implications of FATCA on their investment in our common stock and the entities through which they hold our common stock, including, without limitation, the process and deadlines for meeting the applicable requirements to prevent the imposition of the 30% withholding tax under FATCA.

UNDERWRITERS

Under the terms and subject to the conditions in an underwriting agreement dated the date of this prospectus supplement, the underwriters named below, for whom Morgan Stanley & Co. LLC, Goldman Sachs & Co. LLC and Cowen and Company, LLC are acting as representatives, have severally agreed to purchase, and we have agreed to sell to them, severally, the number of shares indicated below:

Name	Number of Shares
Morgan Stanley & Co. LLC	
Goldman Sachs & Co. LLC	
Cowen and Company, LLC	
Needham & Company, LLC	
Total:	

The underwriters and the representatives are collectively referred to as the "underwriters" and the "representatives," respectively. The underwriters are offering the shares of common stock subject to their acceptance of the shares from us and subject to prior sale. The underwriting agreement provides that the obligations of the several underwriters to pay for and accept delivery of the shares of common stock offered by this prospectus supplement are subject to the approval of certain legal matters by their counsel and to certain other conditions. The underwriters are obligated to take and pay for all of the shares of common stock offered by this prospectus supplement if any such shares are taken. However, the underwriters are not required to take or pay for the shares covered by the underwriters' option to purchase additional shares described below.

The underwriters initially propose to offer part of the shares of common stock directly to the public at the offering price listed on the cover page of this prospectus supplement and part to certain dealers at a price that represents a concession not in excess of $ per share under the public offering price. After the initial offering of the shares of common stock, the offering price and other selling terms may from time to time be varied by the representatives. The offering of the shares by the underwriters is subject to receipt and acceptance and subject to the underwriters' right to reject any order in whole or in part.

We have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus supplement, to purchase up to $22,500,000 of additional shares of common stock at the public offering price listed on the cover page of this prospectus supplement, less underwriting discounts and commissions. To the extent the option is exercised, each underwriter will become obligated, subject to certain conditions, to purchase about the same percentage of the additional shares of common stock as the number listed next to the underwriter's name in the preceding table bears to the total number of shares of common stock listed next to the names of all underwriters in the preceding table.

The following table shows the per share and total public offering price, underwriting discounts and commissions, and proceeds before expenses to us. These amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase up to an additional $22,500,000 of shares of common stock.

		Total	
	Per Share	No Exercise	Full Exercise
Public offering price	$	$	$
Underwriting discounts and commissions to be paid by us			
Proceeds, before expenses, to us	$	$	$

The estimated offering expenses payable by us, exclusive of the underwriting discounts and commissions, are approximately $. We have agreed to reimburse the underwriters for expenses relating to clearance of this offering with the Financial Industry Regulatory Authority up to $40,000.

The underwriters have informed us that they do not intend sales to discretionary accounts to exceed 5% of the total number of shares of common stock offered by them.

Our common stock is listed on the Nasdaq Global Market under the trading symbol "RYTM."

We and all directors, executive officers and certain stockholders have agreed that, without the prior written consent of the representatives on behalf of the underwriters, we and they will not, during the period ending 90 days after the date of this prospectus supplement (the "restricted period"):

- offer, sell, contract to sell, pledge or otherwise dispose of, (or enter into any transaction which is designed to, or might reasonably be expected to, result in the disposition (whether by actual disposition or effective economic disposition due to cash settlement or otherwise), directly or indirectly) any capital stock or any securities convertible into, or exercisable or exchangeable for such capital stock;

- file any registration statement with the SEC (other than a registration statement on Form S-8) relating to the offering of any shares of capital stock or any securities convertible into or exercisable or exchangeable for capital stock; or

- establish or increase a put equivalent position or liquidate or decrease a call equivalent position within the meaning of Section 16 of the Exchange Act and the rules and regulations of the SEC promulgated thereunder with respect to any shares of capital stock or any securities convertible into or exercisable or exchangeable for capital stock;

whether any such transaction described above is to be settled by delivery of common stock or such other securities, in cash or otherwise. In addition, we and each such person agrees that, without the prior written consent of the representatives on behalf of the underwriters, we or such other person will not, during the restricted period, make any demand for, or exercise any right with respect to, the registration of any shares of common stock or any security convertible into or exercisable or exchangeable for common stock.

The restrictions described in the immediately preceding paragraph do not apply to:

- the sale of shares to the underwriters;

- the issuance by us of shares of common stock upon the exercise of an option or a warrant or the conversion of a security outstanding on the date of this prospectus supplement of which the underwriters have been advised in writing;

- transactions by any person other than us relating to shares of common stock or other securities acquired in open market transactions after the completion of the offering of the shares; provided that no filing under Section 16(a) of the Exchange Act, is required or voluntarily made in connection with subsequent sales of the common stock or other securities acquired in such open market transactions; or

- the establishment of a trading plan pursuant to Rule 10b5-1 under the Exchange Act for the transfer of shares of common stock, provided that (i) such plan does not provide for the transfer of common stock during the restricted period and (ii) to the extent a public announcement or filing under the Exchange Act, if any, is required or voluntarily made regarding the establishment of such plan, such announcement or filing shall include a statement to the effect that no transfer of common stock may be made under such plan during the restricted period.

The representatives, in their sole discretion, may release the common stock and other securities subject to the lock-up agreements described above in whole or in part at any time.

In order to facilitate the offering of the common stock, the underwriters may engage in transactions that stabilize, maintain or otherwise affect the price of the common stock. Specifically, the underwriters may sell more shares than they are obligated to purchase under the underwriting agreement, creating a short position. A short sale is covered if the short position is no greater than the number of shares available for purchase by the underwriters under the option. The underwriters can close out a covered short sale by exercising the option or purchasing shares in the open market. In determining the source of shares to close out a covered short sale, the underwriters will consider, among other things, the open market price of shares compared to the price available under the option. The underwriters may also sell shares in excess of the option, creating a naked short position. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market after pricing that could adversely affect investors who purchase in this offering. As an additional means of facilitating this offering, the underwriters may bid for, and purchase, shares of common stock in the open market to stabilize the price of the common stock. These activities may raise or maintain the market price of the common stock above independent market levels or prevent or retard a decline in the market price of the common stock. The underwriters are not required to engage in these activities and may end any of these activities at any time.

The underwriters may also impose a penalty bid. This occurs when a particular underwriter repays to the underwriters a portion of the underwriting discount received by it because the representatives have repurchased shares sold by or for the account of such underwriter in stabilizing or short covering transactions.

We and the underwriters have agreed to indemnify each other against certain liabilities, including liabilities under the Securities Act.

A prospectus supplement in electronic format may be made available on websites maintained by one or more underwriters, or selling group members, if any, participating in this offering. The representatives may agree to allocate a number of shares of common stock to underwriters for sale to their online brokerage account holders. Internet distributions will be allocated by the representatives to underwriters that may make Internet distributions on the same basis as other allocations.

The underwriters and their respective affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, investment research, principal investment, hedging, financing and brokerage activities. Certain of the underwriters and their respective affiliates have, from time to time, performed, and may in the future perform, various financial advisory and investment banking services for us, for which they received or will receive customary fees and expenses.

In addition, in the ordinary course of their various business activities, the underwriters and their respective affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers and may at any time hold long and short positions in such securities and instruments. Such investment and securities activities may involve our securities and instruments. The underwriters and their respective affiliates may also make investment recommendations or publish or express independent research views in respect of such securities or instruments and may at any time hold, or recommend to clients that they acquire, long or short positions in such securities and instruments.

Selling Restrictions

European Economic Area

In relation to each Member State of the European Economic Area (each a "Member State"), no shares of our common stock have been offered or will be offered to the public in that Member State prior to the publication of a prospectus which has been approved by the competent authority in that Member State or, where appropriate, approved in another Member State and notified to the competent authority in that Member State, all in accordance with the Prospectus Regulation, except that offers of shares of our common stock may be made to the public in that Member State at any time under the following exemptions under the Prospectus Regulation:

(a) to any legal entity which is a qualified investor as defined under the Prospectus Regulation;

(b) to fewer than 150 natural or legal persons (other than qualified investors as defined under the Prospectus Regulation), subject to obtaining the prior consent of the representatives for any such offer; or

(c) in any other circumstances falling within Article 1(4) of the Prospectus Regulation,

provided, that no such offer of shares of our common stock shall require the Company or any representative to publish a prospectus pursuant to Article 3 of the Prospectus Regulation or supplement a prospectus pursuant to Article 23 of the Prospectus Regulation.

For the purposes of this provision, an "offer to the public" in relation to any shares of our common stock in any Member State means the communication in any form and by any means of sufficient information on the terms of the offer and any shares of our common stock to be offered so as to enable an investor to decide to purchase or subscribe for any shares of our common stock, and "Prospectus Regulation" means Regulation (EU) 2017/1129.

United Kingdom

Each underwriter has represented and agreed that:

(a) it has only communicated or caused to be communicated and will only communicate or cause to be communicated an invitation or inducement to engage in investment activity (within the meaning of Section 21 of the Financial Services and Markets Act 2000 ("FSMA") received by it in connection with the issue or sale of the shares of our common stock in circumstances in which Section 21(1) of the FSMA does not apply to us; and

(b) it has complied and will comply with all applicable provisions of the FSMA with respect to anything done by it in relation to the shares of our common stock in, from or otherwise involving the United Kingdom.

Canada

The shares may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 Prospectus Exemptions or subsection 73.3(1) of the Securities Act (Ontario), and are permitted clients, as defined in National Instrument 31-103 Registration Requirements, Exemptions and Ongoing Registrant Obligations. Any resale of the shares must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The

purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 (or, in the case of securities issued or guaranteed by the government of a non-Canadian jurisdiction, section 3A.4) of National Instrument 33-105 Underwriting Conflicts (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

Notice to Prospective Investors in Switzerland

The shares may not be publicly offered in Switzerland and will not be listed on the SIX Swiss Exchange, or SIX, or on any other stock exchange or regulated trading facility in Switzerland. This document has been prepared without regard to the disclosure standards for issuance prospectuses under art. 652a or art. 1156 of the Swiss Code of Obligations or the disclosure standards for listing prospectuses under art. 27 ff. of the SIX Listing Rules or the listing rules of any other stock exchange or regulated trading facility in Switzerland. Neither this document nor any other offering or marketing material relating to the shares or the offering may be publicly distributed or otherwise made publicly available in Switzerland.

Neither this document nor any other offering or marketing material relating to the offering, the Company or the shares have been or will be filed with or approved by any Swiss regulatory authority. In particular, this document will not be filed with, and the offer of shares will not be supervised by, the Swiss Financial Market Supervisory Authority, or FINMA, and the offer of shares has not been and will not be authorized under the Swiss Federal Act on Collective Investment Schemes, or CISA. The investor protection afforded to acquirers of interests in collective investment schemes under the CISA does not extend to acquirers of shares.

Notice to Prospective Investors in the Dubai International Financial Centre

This prospectus relates to an Exempt Offer in accordance with the Offered Securities Rules of the Dubai Financial Services Authority, or DFSA. This prospectus is intended for distribution only to persons of a type specified in the Offered Securities Rules of the DFSA. It must not be delivered to, or relied on by, any other person. The DFSA has no responsibility for reviewing or verifying any documents in connection with Exempt Offers. The DFSA has not approved this prospectus nor taken steps to verify the information set forth herein and has no responsibility for the prospectus. The shares to which this prospectus relates may be illiquid and/or subject to restrictions on their resale. Prospective purchasers of the shares offered should conduct their own due diligence on the shares. If you do not understand the contents of this prospectus you should consult an authorized financial advisor.

Notice to Prospective Investors in Singapore

This prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of Non-CIS Securities may not be circulated or distributed, nor may the Non-CIS Securities be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore, or SFA, (ii) to a relevant person pursuant to Section 275(1), or any person pursuant to Section 275(1A), and in accordance with the conditions specified in Section 275, of the SFA, or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA.

Where the Non-CIS Securities are subscribed or purchased under Section 275 of the SFA by a relevant person which is:

(a) a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or

(b) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary of the trust is an individual who is an accredited investor,

securities (as defined in Section 239(1) of the SFA) of that corporation or the beneficiaries' rights and interest (howsoever described) in that trust shall not be transferred within six months after that corporation or that trust has acquired the Non-CIS Securities pursuant to an offer made under Section 275 of the SFA except:

(a) to an institutional investor or to a relevant person defined in Section 275(2) of the SFA, or to any person arising from an offer referred to in Section 275(1A) or Section 276(4)(i)(B) of the SFA;

(b) where no consideration is or will be given for the transfer;

(c) where the transfer is by operation of law;

(d) as specified in Section 276(7) of the SFA; or

(e) as specified in Regulation 32 of the Securities and Futures (Offers of Investments) (Shares and Debentures) Regulations 2005 of Singapore.

Notice to Prospective Investors in Hong Kong

The securities have not been offered or sold and will not be offered or sold in Hong Kong, by means of any document, other than (a) to "professional investors" as defined in the Securities and Futures Ordinance (Cap. 571) of Hong Kong and any rules made under that Ordinance; or (b) in other circumstances which do not result in the document being a "prospectus" as defined in the Companies Ordinance (Cap. 32) of Hong Kong or which do not constitute an offer to the public within the meaning of that Ordinance. No advertisement, invitation or document relating to the securities has been or may be issued or has been or may be in the possession of any person for the purposes of issue, whether in Hong Kong or elsewhere, which is directed at, or the contents of which are likely to be accessed or read by, the public of Hong Kong (except if permitted to do so under the securities laws of Hong Kong) other than with respect to securities which are or are intended to be disposed of only to persons outside Hong Kong or only to "professional investors" as defined in the Securities and Futures Ordinance and any rules made under that Ordinance.

Notice to Prospective Investors in Japan

The securities have not been and will not be registered under the Financial Instruments and Exchange Law of Japan (Law No. 25 of 1948, as amended) and, accordingly, will not be offered or sold, directly or indirectly, in Japan, or for the benefit of any Japanese Person or to others for re-offering or resale, directly or indirectly, in Japan or to any Japanese Person, except in compliance with all applicable laws, regulations and ministerial guidelines promulgated by relevant Japanese governmental or regulatory authorities in effect at the relevant time. For the purposes of this paragraph, "Japanese Person" shall mean any person resident in Japan, including any corporation or other entity organized under the laws of Japan.

Notice to Prospective Investors in Australia

No placement document, prospectus, product disclosure statement or other disclosure document has been lodged with the Australian Securities and Investments Commission, in relation to the offering. This

prospectus does not constitute a prospectus, product disclosure statement or other disclosure document under the Corporations Act 2001, or Corporations Act, and does not purport to include the information required for a prospectus, product disclosure statement or other disclosure document under the Corporations Act.

Any offer in Australia of the shares may only be made to persons, or Exempt Investors, who are "sophisticated investors" (within the meaning of section 708(8) of the Corporations Act), "professional investors" (within the meaning of section 708(11) of the Corporations Act) or otherwise pursuant to one or more exemptions contained in section 708 of the Corporations Act so that it is lawful to offer the shares without disclosure to investors under Chapter 6D of the Corporations Act.

The shares applied for by Exempt Investors in Australia must not be offered for sale in Australia in the period of 12 months after the date of allotment under the offering, except in circumstances where disclosure to investors under Chapter 6D of the Corporations Act would not be required pursuant to an exemption under section 708 of the Corporations Act or otherwise or where the offer is pursuant to a disclosure document which complies with Chapter 6D of the Corporations Act. Any person acquiring shares must observe such Australian on-sale restrictions.

This prospectus contains general information only and does not take account of the investment objectives, financial situation or particular needs of any particular person. It does not contain any securities recommendations or financial product advice. Before making an investment decision, investors need to consider whether the information in this prospectus is appropriate to their needs, objectives and circumstances, and, if necessary, seek expert advice on those matters.

Notice to Prospective Investors in Israel

In the State of Israel this prospectus shall not be regarded as an offer to the public to purchase shares of common stock under the Israeli Securities Law, 5728 - 1968, which requires a prospectus to be published and authorized by the Israel Securities Authority, if it complies with certain provisions of Section 15 of the Israeli Securities Law, 5728 - 1968, including, inter alia, if: (i) the offer is made, distributed or directed to not more than 35 investors, subject to certain conditions (the "Addressed Investors"); or (ii) the offer is made, distributed or directed to certain qualified investors defined in the First Addendum of the Israeli Securities Law, 5728 - 1968, subject to certain conditions (the "Qualified Investors"). The Qualified Investors shall not be taken into account in the count of the Addressed Investors and may be offered to purchase securities in addition to the 35 Addressed Investors. The company has not and will not take any action that would require it to publish a prospectus in accordance with and subject to the Israeli Securities Law, 5728 - 1968. We have not and will not distribute this prospectus or make, distribute or direct an offer to subscribe for our common stock to any person within the State of Israel, other than to Qualified Investors and up to 35 Addressed Investors.

Qualified Investors may have to submit written evidence that they meet the definitions set out in of the First Addendum to the Israeli Securities Law, 5728 - 1968. In particular, we may request, as a condition to be offered common stock, that Qualified Investors will each represent, warrant and certify to us and/or to anyone acting on our behalf: (i) that it is an investor falling within one of the categories listed in the First Addendum to the Israeli Securities Law, 5728 - 1968; (ii) which of the categories listed in the First Addendum to the Israeli Securities Law, 5728 - 1968 regarding Qualified Investors is applicable to it; (iii) that it will abide by all provisions set forth in the Israeli Securities Law, 5728 - 1968 and the regulations promulgated thereunder in connection with the offer to be issued common stock; (iv) that the shares of common stock that it will be issued are, subject to exemptions available under the Israeli Securities Law, 5728 - 1968: (a) for its own account; (b) for investment purposes only; and (c) not issued with a view to resale within the State of Israel, other than in accordance with the provisions of the Israeli Securities Law, 5728 - 1968; and (v) that it is willing to provide further evidence of its Qualified Investor status. Addressed Investors may have to submit written evidence in respect of their identity and may have to sign and submit a declaration containing, inter alia, the Addressed Investor's name, address and passport number or Israeli identification number.

LEGAL MATTERS

Certain legal matters in connection with the shares of common stock offered hereby will be passed upon for us by Morgan, Lewis & Bockius LLP, Boston, Massachusetts. The underwriters are being represented by Ropes & Gray LLP, Boston, Massachusetts, in connection with this offering.

EXPERTS

The consolidated financial statements of Rhythm Pharmaceuticals, Inc. appearing in Rhythm Pharmaceutical's Annual Report (Form 10-K) for the year ended December 31, 2018, have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon included therein, and incorporated herein by reference. Such financial statements are, and audited financial statements to be included in subsequently filed documents will be, incorporated herein in reliance upon the reports of Ernst & Young LLP pertaining to such financial statements (to the extent covered by consents filed with the Securities and Exchange Commission) given on the authority of such firm as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We are subject to the information requirements of the Exchange Act, and in accordance with the Exchange Act, file annual, quarterly and special reports, proxy statements and other information with the SEC. These documents also may be accessed through the SEC's electronic data gathering, analysis and retrieval system, or EDGAR, via electronic means, including the SEC's home page on the Internet (*www.sec.gov*). Our corporate website address is *www.rhythmtx.com*. Information contained on or accessible through our website is not a part of this prospectus supplement, and the inclusion of our website address in this prospectus supplement is an inactive textual reference only.

This prospectus supplement and the accompanying prospectus form part of the registration statement on Form S-3 we filed with the SEC under the Securities Act and does not contain all the information set forth in the registration statement. Whenever a reference is made in this prospectus supplement to any of our contracts, agreements or other documents, the reference may not be complete and you should refer to the exhibits that are a part of the registration statement or the exhibits to the reports or other documents incorporated by reference into this prospectus supplement for a copy of such contract, agreement or other document.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to incorporate by reference into this prospectus supplement the information contained in documents that we file with them, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus supplement. Information in this prospectus supplement supersedes information incorporated by reference that we filed with the SEC before the date of this prospectus supplement, while information that we file later with the SEC will automatically update and supersede prior information. Any information so updated and superseded shall not be deemed, except as so updated and superseded, to constitute a part of this prospectus supplement. We incorporate by reference the documents listed below and any future filings we will make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, prior to the termination of the offering. Notwithstanding the foregoing, unless specifically stated to the contrary, none of the information that is not deemed "filed" with the SEC, including information furnished under Items 2.02 or 7.01 of any Current Report on Form 8-K, will be incorporated by reference into, or otherwise included in, this prospectus supplement.

We incorporate by reference the documents listed below, all filings filed by us pursuant to the Exchange Act after the date of the registration statement of which this prospectus supplement forms a part, and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange

Act prior to the time that all securities covered by this prospectus supplement have been sold; provided, however, that we are not incorporating any documents or information deemed to have been furnished and not filed in accordance with SEC rules:

- our Annual Report on Form 10-K for the fiscal year ended December 31, 2018, filed with the SEC on March 8, 2019;
- the information specifically incorporated by reference into our Annual Report on Form 10-K for the fiscal year ended December 31, 2018 from our definitive proxy statement on Schedule 14A (other than information furnished rather than filed), which was filed with the SEC on April 30, 2019;
- our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2019 and June 30, 2019, filed with the SEC on May 3, 2019 and July 29, 2019, respectively;
- our Current Reports on Form 8-K filed on March 28, 2019, May 23, 2019, June 21, 2019, July 25, 2019 and August 7, 2019; and
- the description of our common stock contained in our Registration Statement on Form 8-A, filed on September 29, 2017, including any amendments thereto or reports filed for the purposes of updating this description.

In addition, all documents subsequently filed by us pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act before the date our offering is terminated or completed are deemed to be incorporated by reference into, and to be a part of, this prospectus supplement.

Any statement contained in this prospectus supplement or in a document incorporated or deemed to be incorporated by reference into this prospectus supplement will be deemed to be modified or superseded for purposes of this prospectus supplement to the extent that a statement contained in this prospectus supplement or any other subsequently filed document that is deemed to be incorporated by reference into this prospectus supplement modifies or supersedes the statement. Any statement so modified or superseded will not be deemed, except as so modified or superseded, to constitute a part of this prospectus supplement.

We will provide to each person, including any beneficial holder, to whom a prospectus supplement is delivered, at no cost, upon written or oral request, a copy of any or all of the information that has been incorporated by reference in the prospectus supplement but not delivered with the prospectus supplement. You should direct any requests for copies to us at Attention: Secretary, 222 Berkeley Street, Boston, MA, 02116 or you may call us at (857) 264-4280. Exhibits to the filings will not be sent, however, unless those exhibits have specifically been incorporated by reference into this prospectus supplement and accompanying prospectus.

You should rely only on information contained in, or incorporated by reference into, this prospectus supplement and the accompanying prospectus. We have not, and the underwriters have not, authorized anyone to provide you with information different from that contained in this prospectus supplement or the accompanying prospectus, or incorporated by reference in this prospectus supplement or the accompanying prospectus and in any free writing prospectus that we have authorized for use in connection with this offering. We and the underwriters are not making offers to sell the securities in any jurisdiction in which such an offer or solicitation is not authorized or in which the person making such offer or solicitation is not qualified to do so or to anyone to whom it is unlawful to make such offer or solicitation.

PROSPECTUS

Common Stock
Preferred Stock
Warrants
Debt Securities
Units

From time to time, we may offer and sell any combination of the securities described in this prospectus, either individually or in combination, at prices and on terms described in one or more supplements to this prospectus. Selling stockholders to be named in a supplement to this prospectus may also from time to time offer and sell shares of our common stock, in one or more offerings.

We may also offer securities as may be issuable upon conversion, redemption, repurchase, exchange or exercise of any securities registered hereunder, including any applicable antidilution provisions. We or any selling stockholder may sell the securities to or through underwriters and also to other purchasers or through agents, on a continuous or delayed basis. The names of any underwriters or agents, and any fees, conversions, or discount arrangements will be set forth in the applicable prospectus supplement accompanying this prospectus. The price to the public of such securities and the net proceeds that we or the selling stockholders expect to receive from such sale will also be set forth in a prospectus supplement. Unless the applicable prospectus supplement provides otherwise, we will not receive any proceeds from the sale of securities by selling stockholders.

This prospectus provides a general description of the securities we may offer. We will provide the specific terms of these offerings in one or more supplements to this prospectus. We may also authorize one or more free writing prospectuses to be provided to you in connection with these offerings. The prospectus supplement and any related free writing prospectus may also add, update or change information contained in this prospectus. You should carefully read this prospectus, the applicable prospectus supplement and any related free writing prospectus, as well as any documents incorporated by reference, before buying any of the securities being offered. **This prospectus may not be used to consummate a sale of securities unless it is accompanied by the applicable prospectus supplement.**

Our common stock is listed on the Nasdaq Global Market under the symbol "RYTM." On November 8, 2018, the closing price for our common stock, as reported on the Nasdaq Global Market, was $31.34 per share.

We are an "emerging growth company" as defined under the federal securities laws and, as such, have elected to comply with certain reduced public company reporting requirements.

Investing in our securities involves a high degree of risk. You should review carefully the risks and uncertainties described under the heading "Risk Factors" contained in this prospectus beginning on page 4 and any applicable prospectus supplement and in any free writing prospectuses we have authorized for use in connection with a specific offering, and under similar headings in the other documents that are incorporated by reference into this prospectus.

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

The date of this prospectus is November 9, 2018.

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ABOUT THIS PROSPECTUS

This prospectus is part of an automatic registration statement on Form S-3 that we filed with the Securities and Exchange Commission, or SEC, using a "shelf" registration process as a "well-known seasoned issuer" as defined in Rule 405 under the Securities Act of 1933, as amended, or the Securities Act. Under this shelf registration statement, we may sell common stock, preferred stock, various series of debt securities, or warrants to purchase any of such securities, either individually or in combination with other securities described in this prospectus, in one or more offerings from time to time. Selling stockholders may offer and sell, in one or more offerings, shares of our common stock as described in this prospectus or the applicable prospectus supplement. There is no limit on the aggregate amount of the securities that we or selling stockholders may offer pursuant to the registration statement of which this prospectus is a part. This prospectus provides you with a general description of the securities we, and the common stock selling stockholders, may offer.

Each time we sell any type or series of securities, or selling stockholders offer common stock, under this prospectus, we will provide a prospectus supplement that will include more specific information about the terms of that offering. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to these offerings. The prospectus supplement and any related free writing prospectus that we may authorize to be provided to you may also add, update or change any of the information contained in this prospectus or in the documents we have incorporated by reference into this prospectus. This prospectus, together with the applicable prospectus supplement, any related free writing prospectus and the documents incorporated by reference into this prospectus and the applicable prospectus supplement, will include all material information relating to the applicable offering. Before buying any of the securities being offered, we urge you to carefully read this prospectus, the applicable prospectus supplement and any related free writing prospectuses we have authorized for use in connection with a specific offering, together with the additional information incorporated herein by reference as described under the heading "Incorporation of Certain Information by Reference."

This prospectus may not be used to consummate a sale of securities unless it is accompanied by a prospectus supplement.

You should rely only on the information we have provided or incorporated by reference in this prospectus or any prospectus supplement. We have not authorized anyone to provide you with information different from that contained or incorporated by reference in this prospectus. No dealer, salesperson or other person is authorized to give any information or to represent anything not contained or incorporated by reference in this prospectus. You must not rely on any unauthorized information or representation. This prospectus is an offer to sell only the securities offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so. You should assume that the information in this prospectus or any prospectus supplement is accurate only as of the date on the front of the document and that any information we have incorporated herein by reference is accurate only as of the date of the document incorporated by reference, regardless of the time of delivery of this prospectus or any sale of a security.

The information appearing in this prospectus, any applicable prospectus supplement and any related free writing prospectus is accurate only as of the date on the front of the document and any information we have incorporated by reference is accurate only as of the date of the document incorporated by reference, regardless of the time of delivery of this prospectus, the prospectus supplement or any related free writing prospectus, or the time of any sale of a security.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference in the accompanying prospectus were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

This prospectus includes summaries of certain provisions contained in some of the documents described herein, but reference is made to the actual documents for complete information. All of the summaries are qualified in their entirety by the actual documents. Copies of some of the documents referred to herein have been filed, will be filed or will be incorporated by reference as exhibits to the registration statement of which this prospectus is a part, and you may obtain copies of those documents as described under the heading "Where You Can Find More Information."

Unless otherwise stated, all references to "us," "our," "RYTM," "we," the "Company" and similar designations refer to Rhythm Pharmaceuticals, Inc. or our predecessor company, as the context may require. Our principal executive offices are located at 500 Boylston Street, 11th Floor, Boston, MA 02116, and our telephone number is (857) 264-4280.

PROSPECTUS SUMMARY

The following summary highlights selected information contained or incorporated by reference elsewhere in this prospectus and does not contain all of the information that you should consider in making your investment decision. Before investing in our securities, you should carefully read this entire prospectus, the applicable prospectus supplement and any related free writing prospectus, including the information under the caption "Risk Factors" herein and the applicable prospectus supplement and under similar headings in the other documents that are incorporated by reference into this prospectus. You should also carefully read the other information incorporated by reference into this prospectus, including our financial statements and the related notes, and the exhibits to the registration statement of which this prospectus is a part.

Our Company

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

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

with setmelanotide in previous and ongoing clinical trials in which setmelanotide demonstrated statistically significant weight loss with good tolerability.

Our common stock is listed on the Nasdaq Global Market under the symbol "RYTM."

Corporate Information

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.

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

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

Implications of Being an Emerging Growth Company

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

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

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

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

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

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

RISK FACTORS

Investing in our securities involves a high degree of risk. Before deciding whether to invest in our securities, you should carefully consider the risks described in the documents incorporated by reference in this prospectus and any applicable prospectus supplement and any related free writing prospectus, as well as other information we include or incorporate by reference into this prospectus and any applicable prospectus supplement, before making an investment decision. Our business, financial condition or results of operations could be materially adversely affected by any of these risks. The trading price of our securities could decline due to the occurrence of any of these risks, and you may lose all or part of your investment. This prospectus and the documents incorporated herein by reference also contain forward-looking statements that involve risks and uncertainties. Actual results could differ materially from those anticipated in these forward-looking statements as a result of certain factors, including the risks described above and in the documents incorporated herein by reference, including in our most recent quarterly report on Form 10-Q on file with the SEC and any amendments thereto reflected in subsequent filings with the SEC, all of which are incorporated by reference into this prospectus in their entirety, together with other information in this prospectus, the documents incorporated by reference and any free writing prospectus that we may authorize for use in connection with a specific offering.

CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING STATEMENTS

This prospectus, including the information incorporated by reference into this prospectus, contains, and any prospectus supplement may contain "forward-looking statements" within the meaning of Section 27A of the Securities Act and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. You can identify these forward-looking statements by the use of words such as "outlook," "believes," "expects," "potential," "continues," "may," "will," "should," "seeks," "approximately," "predicts," "intends," "plans," "estimates," "anticipates" or the negative version of these words or other comparable words. These statements relate to future events or to our future operating or financial performance and involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements. We believe these factors include:

- the success, cost and timing of our product development activities and clinical trials;
- our ability to obtain and maintain regulatory approval for setmelanotide and our future product candidates, if any, and any related restrictions, limitations, and/or warnings in the label of an approved product candidate;
- our ability to obtain funding for our operations;
- the commercialization of setmelanotide, if approved;
- the number of people in our target patient population;
- our plans to research, develop and commercialize setmelanotide;
- our ability to operate, and the implementation of our business strategy, as an independent company;
- our ability to attract collaborators with development, regulatory and commercialization expertise;
- our expectations regarding our ability to obtain and maintain intellectual property protection for setmelanotide;
- future agreements with third parties in connection with the commercialization of setmelanotide or our future product candidates, if any;

- the size and growth potential of the markets for setmelanotide, and our ability to serve those markets;
- our expectations for the pricing of setmelanotide;
- the rate and degree of market acceptance of setmelanotide, as well as the reimbursement coverage for setmelanotide;
- regulatory developments in the United States, the European Union and other jurisdictions;
- the performance of our third-party suppliers and manufacturers;
- the extent and success of competing therapies that are or may become available;
- our ability to attract and retain key scientific or management personnel;
- the accuracy of our estimates regarding our target patient populations, expenses, future revenues, capital requirements and needs for additional financing;
- our expectations regarding the period during which we qualify as an emerging growth company under the JOBS Act; and
- our use of the proceeds from this offering.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important cautionary statements in this prospectus or in the documents incorporated by reference in this prospectus, particularly in the "Risk Factors" section, that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. For a summary of such factors, please refer to the section entitled "Risk Factors" in this prospectus, as updated and supplemented by the discussion of risks and uncertainties under "Risk Factors" contained in any supplements to this prospectus and in our most recent annual report on Form 10-K, as revised or supplemented by our subsequent quarterly reports on Form 10-Q or our current reports on Form 8-K, as well as any amendments thereto, as filed with the SEC and which are incorporated herein by reference.

In light of these assumptions, risks and uncertainties, the results and events discussed in the forward-looking statements contained in this prospectus, any prospectus supplement or in any document incorporated herein by reference might not occur. Investors are cautioned not to place undue reliance on the forward-looking statements, which speak only as of the date of this prospectus, any prospectus supplement or the date of the document incorporated by reference in this prospectus. We are not under any obligation, and we expressly disclaim any obligation, to update or alter any forward-looking statements, whether as a result of new information, future events or otherwise. All subsequent forward-looking statements attributable to us or to any person acting on our behalf are expressly qualified in their entirety by the cautionary statements contained or referred to in this section.

USE OF PROCEEDS

Except as described in any applicable prospectus supplement or in any related free writing prospectuses we may authorize for use in connection with a specific offering, we currently intend to use the net proceeds from the sale of the securities offered by us hereunder, if any, for working capital and general corporate purposes, including research and development expenses, and selling, general and administrative expenses. As of the date of this prospectus, we cannot specify with certainty all of the particular uses for the net proceeds to us from the sale of the securities offered by us hereunder. We will set forth in the applicable prospectus supplement or free writing prospectus our intended use for the net proceeds received from the sale of any securities sold pursuant to the prospectus supplement or free writing prospectus.

Shares of our common stock may be offered by selling stockholders under an applicable prospectus supplement to this prospectus. Unless the applicable prospectus supplement provides otherwise, we will not receive any of the proceeds from the sale or other disposition of shares of our common stock sold by selling stockholders in any offering by them.

THE SECURITIES WE MAY OFFER

We may offer shares of our common stock and preferred stock, various series of warrants to purchase common stock or preferred stock, debt securities, in one or more series, as either senior or subordinated debt or as senior or subordinated convertible debt, units or any combination thereof, and any selling stockholder may offer shares of our common stock, from time to time in one or more offerings under this prospectus at prices and on terms to be determined at the time of any offering. This prospectus provides you with a general description of the securities we and any selling stockholder may offer. Each time we or any selling stockholder offer a type or series of securities under this prospectus, we will provide a prospectus supplement or free writing prospectus, or both, that will describe the specific amounts, prices and other important terms of the securities.

DESCRIPTION OF CAPITAL STOCK

The following is a description of certain provisions of our amended and restated certificate of incorporation and amended and restated bylaws, and certain provisions of the Delaware General Corporation Law, or DGCL. The following description does not purport to be complete and is subject to, and qualified in its entirety by reference to, our amended and restated certificate of incorporation and amended and restated bylaws, each filed as exhibits to the registration statement of which this prospectus forms a part, and the terms and provisions of the DGCL. For more complete information, you should carefully review our amended and restated certificate of incorporation and amended and restated bylaws, which have been filed with the SEC as exhibits to our registration statement of which this prospectus forms a part and which may be obtained as described below under "Where You Can Find More Information."

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

As of September 30, 2018, there were 34,382,525 shares of our common stock outstanding, held by approximately 22 stockholders of record, and there were no shares of preferred stock outstanding.

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 Nasdaq, which apply so long as our common stock remains listed on Nasdaq, require stockholder approval of certain issuances equal to or exceeding 20% of the then outstanding voting power or then outstanding number of shares of common stock. These additional shares may be used for a variety of corporate purposes, including future public offerings, to raise additional capital or to facilitate acquisitions.

One of the effects of the existence of unissued and unreserved common stock or preferred stock may be to enable our board of directors to issue shares to persons friendly to current management, which issuance could render more difficult or discourage an attempt to obtain control of our company by means of a merger, tender offer, proxy contest or otherwise, and thereby protect the continuity of our management and possibly deprive our stockholders of opportunities to sell their shares of common stock at prices higher than prevailing market prices.

Anti-Takeover Effects of Provisions of Delaware Law and Our Amended and Restated Certificate of Incorporation and Amended and Restated Bylaws

Undesignated Preferred Stock

The ability to authorize undesignated preferred stock will make it possible for our board of directors to issue preferred stock with super voting, special approval, dividend or other rights or preferences on a discriminatory basis that could impede the success of any attempt to acquire us or otherwise effect a change in control of us. These and other provisions may have the effect of deferring, delaying or discouraging hostile takeovers, or changes in control or management of our company.

Requirements for Advance Notification of Stockholder Meetings, Nominations and Proposals

Our amended and restated certificate of incorporation provides that special meetings of the stockholders may be called only by or at the direction of our board of directors. Our amended and restated bylaws prohibit the conduct of any business at a special meeting other than as specified in the notice for such meeting. These provisions may have the effect of deferring, delaying or discouraging hostile takeovers, or changes in control or management of our company.

Our amended and restated bylaws establish advance notice procedures with respect to stockholder proposals and the nomination of candidates for election as directors, other than nominations made by or at the direction of the board of directors or a committee of the board of directors. In order for any matter to be "properly brought" before a meeting, a stockholder will have to comply with advance notice requirements and provide us with certain information. Additionally, vacancies and newly created directorships may be filled only by a vote of a majority of the directors then in office, even though less than a quorum, and not by the stockholders. Our amended and restated bylaws allow the presiding officer at a meeting of the stockholders to adopt rules and regulations for the conduct of meetings which may have the effect of precluding the conduct of certain business at a meeting if the rules and regulations are not followed. These provisions may also defer, delay or discourage a potential acquirer from conducting a solicitation of proxies to elect the acquirer's own slate of directors or otherwise attempting to obtain control of our company.

Our amended and restated certificate of incorporation provides that the board of directors is expressly authorized to adopt, amend or repeal our amended and restated bylaws.

No Cumulative Voting

The DGCL provides that stockholders are not entitled to cumulate votes in the election of directors unless our amended and restated certificate of incorporation provides otherwise. Our amended and restated certificate of incorporation does not expressly provide for cumulative voting.

Removal of Directors

In accordance with the terms of our amended and restated certificate of incorporation and amended and restated bylaws, our board of directors are divided into three staggered classes of directors of the same or nearly the same number. At each annual meeting of the stockholders, a class of directors will be elected for a three-year term to succeed the directors of the same class whose terms are then expiring.

- Our Class I directors are Keith Gottesdiener and Christophe Jean, whose terms expire in 2021;
- Our Class II directors are Ed Mathers, Todd Foley, and Neil Exter, whose terms expire in 2019; and
- Our Class III directors are David Meeker and David McGirr, whose terms expire in 2020.

Our amended and restated certificate of incorporation and amended and restated bylaws provide that the number of our directors shall be fixed from time to time by a resolution of the majority of our board of directors. Any additional directorships resulting from an increase in the number of directors will be distributed among the three classes so that, as nearly as possible, each class shall consist of one third of the board of directors.

The division of our board of directors into three classes with staggered three-year terms may delay or prevent stockholder efforts to effect a change of our management or a change in control.

Our amended and restated certificate of incorporation and amended and restated bylaws provide that our directors may be removed only for cause by the affirmative vote of the holders of at least 75% of the outstanding shares of capital stock entitled to vote in the election of directors or class of directors, voting together as a single class, at a meeting of the stockholders called for that purpose. This requirement of a supermajority vote to remove directors could enable a minority of our stockholders to prevent a change in the composition of our board. Any vacancy on our board of directors, including a vacancy resulting from an enlargement of our board of directors, may be filled only by the vote of a majority of the remaining directors then in office, although less than a quorum, or by the sole remaining director.

Amendments to Amended and Restated Certificate of Incorporation and Amended and Restated Bylaws

The DGCL provides that, unless a corporation's certificate of incorporation provides otherwise, the affirmative vote of holders of shares constituting a majority of the votes of all shares entitled to vote may approve amendments to the certificate of incorporation.

Our amended and rested certificate of incorporation and amended and restated bylaws provide that the affirmative vote of holders of at least 75% of the outstanding shares of capital stock, voting together as a single class, and entitled to vote in the election of directors will be required to amend, alter, change or repeal the amended and restated certificate of incorporation and the amended and restated bylaws. This requirement of a supermajority vote to approve amendments to our amended and restated certificate of incorporation and amended and restated bylaws could enable a minority of our stockholders to exercise veto power over such amendments.

Stockholder Action by Written Consent

Pursuant to Section 228 of the DGCL, any action required to be taken at any annual or special meeting of the stockholders may be taken without a meeting, without prior notice and without a vote if a consent or consents in writing, setting forth the action so taken, is signed by the holders of outstanding stock having not less than the minimum number of votes that would be necessary to authorize or take such action at a meeting at which all shares of our stock entitled to vote thereon were present and voted, unless the corporation's certificate of incorporation provides otherwise. Our amended and restated certificate of incorporation prohibits the taking of any action of our stockholders by written consent without a meeting.

Delaware Anti-Takeover Statute

We have not opted out of, and therefore are subject to, Section 203 of the DGCL. Section 203 provides that, subject to certain exceptions specified in the law, a publicly-held Delaware corporation shall not engage in certain "business combinations" with any "interested stockholder" for a three-year period after the date of the transaction in which the person became an interested stockholder unless:

- prior to the date of the transaction, the board of directors of the corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder;
- upon completion of the transaction that resulted in the stockholder becoming an interested stockholder, the stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the number of shares outstanding (1) shares owned by persons who are directors and also officers and (2) shares owned under employee stock plans in which employee participants

do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or

- on or subsequent to the date of the transaction, the business combination is approved by the board and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least 66 2/3% of the outstanding voting stock which is not owned by the interested stockholder.

Generally, a business combination includes a merger, asset or stock sale, or other transaction resulting in a financial benefit to the interested stockholder. An interested stockholder is a person who, together with affiliates and associates, owns or, within three years prior to the determination of interested stockholder status, did own 15% or more of a corporation's outstanding voting stock. Since Section 203 will apply to us, we expect that it would have an anti-takeover effect with respect to transactions our board of directors does not approve in advance. In such event, we would also anticipate that Section 203 could discourage attempts that might result in a premium over the market price for the shares of common stock held by stockholders.

Under certain circumstances, Section 203 makes it more difficult for a person who would be an "interested stockholder" to effect various business combinations with a corporation for a three-year period. The provisions of Section 203 may encourage companies interested in acquiring our company to negotiate in advance with our board of directors because the stockholder approval requirement would be avoided if our board of directors approves either the business combination or the transaction that results in the stockholder becoming an interested stockholder. These provisions also may make it more difficult to accomplish transactions that stockholders may otherwise deem to be in their best interests.

Registration Rights

As of September 30, 2018, the holders of approximately 12.0 million shares of our common stock, or their transferees, are entitled to the registration rights set forth below with respect to registration of the resale of such shares under the Securities Act pursuant to the investors' rights agreement, by and among us and certain of our stockholders.

Demand Registration Rights

Upon the written request of at least a majority of the holders of the registrable securities then outstanding that we file a registration statement under the Securities Act covering the registration of registrable securities owned by such holder(s) having an anticipated aggregate offering price, net of selling expenses, of at least $15.0 million, we will be obligated to notify all holders of registrable securities of such request. As soon as practicable thereafter, and in any event within 60 days after the date such request is received, we will be required to register the sale on a registration statement on Form S-1 of all registrable securities that holders may request to be registered, subject to specified exceptions, conditions and limitations. We may postpone the filing of a registration statement for up to 120 days once in any 12-month period if in the good faith judgment of our board of directors such registration would be materially detrimental to us, and we are not required to effect the filing of a registration statement during the period starting with the date that is 60 days prior to our good faith estimate of the date of filing of a registration statement initiated by us and ending on a date 180 days after the effective date of a registration statement initiated by us. The underwriters of any underwritten offering will have the right to limit the number of shares having registration rights to be included in the registration statement.

"Piggyback" Registration Rights

If we register any securities for public sale, holders of registration rights will have the right to include their shares in the registration statement. The underwriters of any underwritten offering will have the right to limit the number of registrable securities to be included in the registration statement, but such number may not be below 30% of the total number of shares included in such registration statement. The holders of registration rights have waived any and all rights to which they would otherwise be entitled to have their shares included in this offering.

Form S-3 Registration Rights

If we are eligible to file a registration statement on Form S-3, holders of at least 10% of our registrable securities then outstanding have the right to request that we file a registration statement on Form S-3, so long as the aggregate price to the public of the securities to be sold under the registration statement on Form S-3 is at least $10.0 million or consists of all the remaining registrable securities, and subject to specified exceptions, conditions and limitations.

Expenses of Registration

Pursuant to the investors' rights agreement, we are generally required to bear all registration expenses, including the fees and expenses of one counsel, not to exceed $50,000, representing the selling holders, incurred in connection with the demand, piggyback and Form S-3 registrations described above. We are not required to bear selling expenses, which include all underwriting discounts, selling commissions, stock transfer taxes applicable to the sale of registrable securities and fees and disbursements of any additional counsel for any selling holder. We are not required to pay registration expenses if the registration request under the investors' rights agreement is withdrawn at the request of the holders of a majority of the registrable securities unless (i) the holders of a majority of the registrable securities then outstanding agree to forfeit their right to one registration under the investors' rights agreement or (ii) the withdrawal is due to the discovery of a material adverse change in our business.

Termination of Registration Rights

The demand, piggyback and Form S-3 registration rights discussed above will terminate as to a given holder of registrable securities upon the earlier of (i) five years following the closing of our initial public offering or (ii) such time as SEC Rule 144 or another similar exemption under the Securities Act is available for the sale of all shares held by the holder during a three-month period without registration and without the requirement for us to be in compliance with the current public information required under SEC Rule 144(c)(1).

Market Listing

Our common stock is listed on the Nasdaq Global Market under the symbol "RYTM."

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Computershare Trust Company, Inc. The transfer agent and registrar's address is 250 Royall Street, Canton, MA 02021.

DESCRIPTION OF DEBT SECURITIES

The following is a general description of the terms of debt securities we may issue from time to time unless we provide otherwise in the applicable prospectus supplement. Particular terms of any debt securities we offer will be described in the prospectus supplement relating to such debt securities.

As required by Federal law for all bonds and notes of companies that are publicly offered, any debt securities we issue will be governed by a document called an "indenture," the form of which is filed as an exhibit to the registration statement of which this prospectus forms a part. We have summarized the general features of the debt securities to be governed by the indenture. The summary is not complete. An indenture is a contract between us and a financial institution acting as trustee on behalf of the holders of the debt securities, and is subject to and governed by the Trust Indenture Act of 1939, as amended, or the Trust Indenture Act. The trustee has two main roles. First, the trustee can enforce holders' rights against us if we default. There are some limitations on the extent to which the trustee acts on holders' behalf, described in the second paragraph under "Description of Debt Securities—Events of Default." Second, the trustee performs certain administrative duties, such as sending interest and principal payments to holders.

We will issue any senior or subordinated debt securities under a senior or subordinated indenture, as applicable, that we will enter into with the trustee named in the subordinated indenture. We have filed a form of senior indenture and a form of subordinated indenture as exhibits to the registration statement of which this prospectus is a part, and supplemental indentures and forms of debt securities containing the terms of the debt securities being offered will be filed as exhibits to the registration statement of which this prospectus is a part or will be incorporated by reference from reports that we file with the SEC. The indentures will be qualified under the Trust Indenture Act.

Because this section is a summary, it does not describe every aspect of any debt securities we may issue or the indenture governing any such debt securities. Particular terms of any debt securities we offer will be described in the prospectus supplement relating to such debt securities, and we urge you to read the applicable executed indenture, which will be filed with the SEC at the time of any offering of debt securities, because it, and not this description, will define the rights of holders of such debt securities.

A prospectus supplement will describe the particular terms of any series of debt securities we may issue, including some or all of the following:

- the designation or title of the series of debt securities;
- the total principal amount of the series of debt securities, the denominations in which the offered debt securities will be issued and whether the offering may be reopened for additional securities of that series and on what terms;
- the percentage of the principal amount at which the series of debt securities will be offered;
- the date or dates on which principal will be payable;
- the rate or rates (which may be either fixed or variable) and/or the method of determining such rate or rates of interest, if any;
- the date or dates from which any interest will accrue, or the method of determining such date or dates, and the date or dates on which any interest will be payable;
- the terms for redemption, extension or early repayment, if any;
- the currencies in which the series of debt securities are issued and payable;

- whether the amount of payments of principal, interest or premium, if any, on a series of debt securities will be determined with reference to an index, formula or other method and how these amounts will be determined;
- the place or places of payment, transfer, conversion and/or exchange of the debt securities;
- the provision for any sinking fund;
- any restrictive covenants;
- events of default;
- whether the series of debt securities are issuable in certificated form;
- any provisions for legal defeasance or covenant defeasance;
- whether and under what circumstances we will pay additional amounts in respect of any tax, assessment or governmental charge and, if so, whether we will have the option to redeem the debt securities rather than pay the additional amounts (and the terms of this option);
- any provisions for convertibility or exchangeability of the debt securities into or for any other securities;
- whether the debt securities are subject to subordination and the terms of such subordination;
- any listing of the debt securities on any securities exchange;
- if applicable, a discussion of certain U.S. Federal income tax considerations, including those related to original issue discount, if applicable; and
- any other material terms.

The debt securities may be secured or unsecured obligations. Unless the prospectus supplement states otherwise, principal, interest and premium, if any, will be paid by us in immediately available funds.

General

The indenture may provide that any debt securities proposed to be sold under this prospectus and the applicable prospectus supplement relating to such debt securities ("offered debt securities") and any debt securities issuable upon conversion or exchange of other offered securities ("underlying debt securities") may be issued under the indenture in one or more series.

For purposes of this prospectus, any reference to the payment of principal of, or interest or premium, if any, on, debt securities will include additional amounts if required by the terms of the debt securities.

Debt securities issued under an indenture, when a single trustee is acting for all debt securities issued under the indenture, are called the "indenture securities." The indenture may also provide that there may be more than one trustee thereunder, each with respect to one or more different series of securities issued thereunder. See "Description of Debt Securities—Resignation of Trustee" below. At a time when two or more trustees are acting under an indenture, each with respect to only certain series, the term "indenture securities" means the one or more series of debt securities with respect to which each respective trustee is acting. In the event that there is more than one trustee under an indenture, the powers and trust obligations of each trustee described in this prospectus will extend only to the one or more series of indenture securities for which it is trustee. If two or more trustees are acting under an indenture, then the indenture securities for which each trustee is acting would be treated as if issued under separate indentures.

We refer you to the applicable prospectus supplement relating to any debt securities we may issue from time to time for information with respect to any deletions from, modifications of or additions to the Events of Default or covenants that are described below, including any addition of a

covenant or other provision providing event risk or similar protection, that will be applicable with respect to such debt securities.

We have the ability to issue indenture securities with terms different from those of indenture securities previously issued and, without the consent of the holders thereof, to reopen a previous issue of a series of indenture securities and issue additional indenture securities of that series unless the reopening was restricted when that series was created.

Conversion and Exchange

If any debt securities are convertible into or exchangeable for other securities, the related prospectus supplement will explain the terms and conditions of the conversion or exchange, including the conversion price or exchange ratio (or the calculation method), the conversion or exchange period (or how the period will be determined), if conversion or exchange will be mandatory or at the option of the holder or us, provisions for adjusting the conversion price or the exchange ratio and provisions affecting conversion or exchange in the event of the redemption of the underlying debt securities. These terms may also include provisions under which the number or amount of other securities to be received by the holders of the debt securities upon conversion or exchange would be calculated according to the market price of the other securities as of a time stated in the prospectus supplement.

Payment and Paying Agents

We will pay interest to the person listed in the applicable trustee's records as the owner of the debt security at the close of business on a particular day in advance of each due date for interest, even if that person no longer owns the debt security on the interest due date. That day, often approximately two weeks in advance of the interest due date, is called the "record date." Because we will pay all the interest for an interest period to the holders on the record date, holders buying and selling debt securities must work out between themselves the appropriate purchase price. The most common manner is to adjust the sales price of the debt securities to prorate interest fairly between buyer and seller based on their respective ownership periods within the particular interest period. This prorated interest amount is called "accrued interest."

Events of Default

Holders of debt securities of any series will have rights if an Event of Default occurs in respect of the debt securities of such series and is not cured, as described later in this subsection. The term "Event of Default" in respect of the debt securities of any series means any of the following:

- we do not pay the principal of, or any premium on, a debt security of the series on its due date;
- we do not pay interest on a debt security of the series within 30 days of its due date;
- we do not deposit any sinking fund payment in respect of debt securities of the series on its due date and we do not cure this default within five days;
- we remain in breach of a covenant in respect of debt securities of the series for 90 days after we receive a written notice of default stating we are in breach. The notice must be sent by either the trustee or holders of at least 25% of the principal amount of debt securities of the series;
- we file for bankruptcy or certain other events of bankruptcy, insolvency or reorganization occur; and
- any other Event of Default occurs in respect of debt securities of the series described in the prospectus supplement.

An Event of Default for a particular series of debt securities does not necessarily constitute an Event of Default for any other series of debt securities issued under the same or any other indenture. The trustee may withhold notice to the holders of debt securities of any default, except in the payment of principal, premium or interest, if it considers the withholding of notice to be in the best interests of the holders.

Remedies if an Event of Default Occurs

If an Event of Default has occurred and has not been cured or waived, the trustee or the holders of not less than 25% in principal amount of the debt securities of the affected series may declare the entire principal amount of all the debt securities of that series to be due and immediately payable. This is called a declaration of acceleration of maturity. A declaration of acceleration of maturity may be canceled by the holders of a majority in principal amount of the debt securities of the affected series if the default is cured or waived and certain other conditions are satisfied.

Except in cases of default, where the trustee has some special duties, the trustee typically is not required to take any action under an indenture at the request of any holders unless the holders offer the trustee reasonable protection from expenses and liability (called an "indemnity"). If reasonable indemnity is provided, the holders of a majority in principal amount of the outstanding debt securities of the relevant series may direct the time, method and place of conducting any lawsuit or other formal legal action seeking any remedy available to the trustee. The trustee may refuse to follow those directions in certain circumstances.

Before a holder is allowed to bypass the trustee and bring its own lawsuit or other formal legal action or take other steps to enforce its rights or protect its interests relating to any debt securities, the following must occur:

- the holder must give the trustee written notice that an Event of Default has occurred and remains uncured;
- the holders of at least 25% in principal amount of all outstanding debt securities of the relevant series must make a written request that the trustee take action because of the default and must offer reasonable indemnity to the trustee against the cost and other liabilities of taking that action;
- the trustee must not have taken action for 60 days after receipt of the above notice and offer of indemnity; and
- the holders of a majority in principal amount of the debt securities must not have given the trustee a direction inconsistent with the above notice during that 60-day period.

However, a holder is entitled at any time to bring a lawsuit for the payment of money due on its debt securities on or after the due date. Each year, we will furnish to each trustee a written statement of certain of our officers certifying that to their knowledge we are in compliance with the indenture and the debt securities, or else specifying any default.

Waiver of Default

The holders of a majority in principal amount of the relevant series of debt securities may waive a default for all such series of debt securities. If this happens, the default will be treated as if it had not occurred. No one can waive a payment default on a holder's debt security, however, without the holder's approval.

Merger or Consolidation

Under the terms of an indenture, we may be permitted to consolidate or merge with another entity. We may also be permitted to sell all or substantially all of our assets to another entity. However, typically we may not take any of these actions unless all the following conditions are met:

- if we do not survive such transaction or we convey, transfer or lease our properties and assets substantially as an entirety, the acquiring company must be a corporation, limited liability company, partnership or trust, or other corporate form, organized under the laws of any state of the United States or the District of Columbia, and such company must agree to be legally responsible for our debt securities, and, if not already subject to the jurisdiction of any state of the United States or the District of Columbia, the new company must submit to such jurisdiction for all purposes with respect to the debt securities and appoint an agent for service of process;
- alternatively, we must be the surviving company;
- immediately after the transaction no Event of Default will exist;
- we must deliver certain certificates and documents to the trustee; and
- we must satisfy any other requirements specified in the prospectus supplement relating to a particular series of debt securities.

Modification or Waiver

There are three types of changes we may make to an indenture and the debt securities issued thereunder.

Changes Requiring Approval

First, there are changes that we cannot make to debt securities without specific approval of all of the holders. The following is a list of the types of changes that may require specific approval:

- change the stated maturity of the principal of or rate of interest on a debt security;
- reduce any amounts due on a debt security;
- reduce the amount of principal payable upon acceleration of the maturity of a security following a default;
- at any time after a change of control has occurred, reduce any premium payable upon a change of control;
- change the place or currency of payment on a debt security (except as otherwise described in the prospectus or prospectus supplement);
- impair the right of holders to sue for payment;
- adversely affect any right to convert or exchange a debt security in accordance with its terms;
- reduce the percentage of holders of debt securities whose consent is needed to modify or amend the indenture;
- reduce the percentage of holders of debt securities whose consent is needed to waive compliance with certain provisions of the indenture or to waive certain defaults;
- modify any other aspect of the provisions of the indenture dealing with supplemental indentures, modification and waiver of past defaults, changes to the quorum or voting requirements or the waiver of certain covenants; and
- change any obligation we have to pay additional amounts.

Changes Not Requiring Approval

The second type of change does not require any vote by the holders of the debt securities. This type is limited to clarifications and certain other changes that would not adversely affect holders of

the outstanding debt securities in any material respect, including the addition of covenants and guarantees. We also do not need any approval to make any change that affects only debt securities to be issued under the indenture after the change takes effect.

Changes Requiring Majority Approval

Any other change to the indenture and the debt securities may require the following approval:

- if the change affects only one series of debt securities, it must be approved by the holders of a majority in principal amount of that series; and
- if the change affects more than one series of debt securities issued under the same indenture, it must be approved by the holders of a majority in principal amount of all of the series affected by the change, with all affected series voting together as one class for this purpose.

The holders of a majority in principal amount of all of the series of debt securities issued under an indenture, voting together as one class for this purpose, may waive our compliance obligations with respect to some of our covenants in that indenture. However, we cannot obtain a waiver of a payment default or of any of the matters covered by the bullet points included above under "Description of Debt Securities—Modification or Waiver—Changes Requiring Approval."

Further Details Concerning Voting

When taking a vote on proposed changes to the indenture and the debt securities, we expect to use the following rules to decide how much principal to attribute to a debt security:

- for original issue discount securities, we will use the principal amount that would be due and payable on the voting date if the maturity of these debt securities were accelerated to that date because of a default;
- for debt securities whose principal amount is not known (for example, because it is based on an index), we will use a special rule for that debt security described in the related prospectus supplement; and
- for debt securities denominated in one or more foreign currencies, we will use the U.S. dollar equivalent.

Debt securities will not be considered outstanding, and therefore not eligible to vote, if we have deposited or set aside in trust money for their payment or redemption. Debt securities will also not be eligible to vote if they have been fully defeased as described later under "Description of Debt Securities—Defeasance—Legal Defeasance."

We generally will be entitled to set any day as a record date for the purpose of determining the holders of outstanding indenture securities that are entitled to vote or take other action under the indenture. If we set a record date for a vote or other action to be taken by holders of one or more series, that vote or action may be taken only by persons who are holders of outstanding indenture securities of those series on the record date and must be taken within 11 months following the record date.

Book-entry and other indirect holders will need to consult their banks or brokers for information on how approval may be granted or denied if we seek to change the indenture or the debt securities or request a waiver.

Defeasance

The following provisions will be applicable to each series of debt securities unless we state in the applicable prospectus supplement that the provisions of covenant defeasance and legal defeasance will not be applicable to that series.

Covenant Defeasance

We can make the deposit described below and be released from some of the restrictive covenants in the indenture under which the particular series was issued. This is called "covenant defeasance." In that event, the holders would lose the protection of those restrictive covenants but would gain the protection of having money and government securities set aside in trust to repay holders' debt securities. If applicable, a holder also would be released from the subordination provisions described under "Description of Debt Securities—Indenture Provisions—Subordination" below. In order to achieve covenant defeasance, we must do the following:

- If the debt securities of the particular series are denominated in U.S. dollars, we must deposit in trust for the benefit of all holders of such debt securities a combination of money and U.S. government or U.S. government agency notes or bonds that will generate enough cash to make interest, principal and any other payments on the debt securities on their various due dates;
- We may be required to deliver to the trustee a legal opinion of our counsel confirming that, under current U.S. Federal income tax law, we may make the above deposit without causing the holders to be taxed on the debt securities any differently than if we did not make the deposit and just repaid the debt securities ourselves at maturity; and
- We must deliver to the trustee certain documentation stating that all conditions precedent to covenant defeasance have been complied with.

If we accomplish covenant defeasance, holders can still look to us for repayment of the debt securities if there were a shortfall in the trust deposit or the trustee is prevented from making payment. In fact, if one of the remaining Events of Default occurred (such as our bankruptcy) and the debt securities became immediately due and payable, there might be a shortfall. Depending on the event causing the default, holders may not be able to obtain payment of the shortfall.

Legal Defeasance

As described below, we can legally release ourselves from all payment and other obligations on the debt securities of a particular series (called "legal defeasance"), (1) if there is a change in U.S. Federal tax law that allows us to effect the release without causing the holders to be taxed any differently than if the release had not occurred, and (2) if we put in place the following other arrangements for holders to be repaid:

- If the debt securities of the particular series are denominated in U.S. dollars, we must deposit in trust for the benefit of all holders of such debt securities a combination of money and U.S. government or U.S. government agency notes or bonds that will generate enough cash to make interest, principal and any other payments on the debt securities on their various due dates;
- We may be required to deliver to the trustee a legal opinion confirming that there has been a change in current U.S. Federal tax law or an Internal Revenue Service ruling that allows us to make the above deposit without causing the holders to be taxed on the debt securities any differently than if we did not make the deposit and just repaid the debt securities ourselves at maturity. Under current U.S. Federal tax law, the deposit and our legal release from the debt securities would be treated as though we paid each holder its

share of the cash and notes or bonds at the time the cash and notes or bonds were deposited in trust in exchange for its debt securities and holders would recognize gain or loss on the debt securities at the time of the deposit; and

- We must deliver to the trustee a legal opinion and officers' certificate stating that all conditions precedent to legal defeasance have been complied with.

If we ever did accomplish legal defeasance, as described above, holders would have to rely solely on the trust deposit for repayment of the debt securities. Holders could not look to us for repayment in the unlikely event of any shortfall. Conversely, the trust deposit would most likely be protected from claims of our lenders and other creditors if we ever became bankrupt or insolvent. If applicable, holders would also be released from the subordination provisions described later under "Description of Debt Securities—Indenture Provisions—Subordination."

Resignation of Trustee

Each trustee may resign or be removed with respect to one or more series of indenture securities provided that a successor trustee is appointed to act with respect to such series. In the event that two or more persons are acting as trustee with respect to different series of indenture securities under the indenture, each of the trustees will be a trustee of a trust separate and apart from the trust administered by any other trustee.

Indenture Provisions—Subordination

Upon any distribution of our assets upon our dissolution, winding up, liquidation or reorganization, the payment of the principal of (and premium, if any) and interest on any indenture securities denominated as subordinated debt securities is to be subordinated to the extent provided in the indenture in right of payment to the prior payment in full of all Senior Indebtedness (defined below), but our obligation to holders to make payment of the principal of (and premium, if any) and interest on such subordinated debt securities will not otherwise be affected. In addition, no payment on account of principal (or premium, if any), interest or sinking fund, if any, may be made on such subordinated debt securities at any time unless full payment of all amounts due in respect of the principal (and premium, if any), interest and sinking fund, if any, on Senior Indebtedness has been made or duly provided for in money or money's worth.

In the event that, notwithstanding the foregoing, any payment from us is received by the trustee in respect of subordinated debt securities or by the holders of any of such subordinated debt securities before all Senior Indebtedness is paid in full, the payment or distribution must be paid over to the holders of the Senior Indebtedness or on their behalf for application to the payment of all the Senior Indebtedness remaining unpaid until all the Senior Indebtedness has been paid in full, after giving effect to any concurrent payment or distribution to the holders of the Senior Indebtedness. Subject to the payment in full of all Senior Indebtedness, the holders of such subordinated debt securities will be subrogated to the rights of the holders of the Senior Indebtedness to the extent of payments made to the holders of the Senior Indebtedness out of the distributive share of such subordinated debt securities.

By reason of this subordination, in the event of a distribution of our assets upon our insolvency, certain of our senior creditors may recover more, ratably, than holders of any subordinated debt securities. The related indenture will provide that these subordination provisions will not apply to money and securities held in trust under the defeasance provisions of the indenture.

"Senior Indebtedness" will be defined in an applicable indenture as the principal of (and premium, if any) and unpaid interest on:

- our indebtedness (including indebtedness of others guaranteed by us), whenever created, incurred, assumed or guaranteed, for money borrowed (other than indenture securities issued under the indenture and denominated as subordinated debt securities), unless in the instrument creating or evidencing the same or under which the same is outstanding it is provided that this indebtedness is not senior or prior in right of payment to the subordinated debt securities; and
- renewals, extensions, modifications and refinancings of any of such indebtedness.

The prospectus supplement accompanying any series of indenture securities denominated as subordinated debt securities will set forth the approximate amount of our Senior Indebtedness outstanding as of a recent date.

Trustee

We intend to name the indenture trustee for each series of indenture securities in the related prospectus supplement.

Certain Considerations Relating to Foreign Currencies

Debt securities denominated or payable in foreign currencies may entail significant risks. These risks include the possibility of significant fluctuations in the foreign currency markets, the imposition or modification of foreign exchange controls and potential illiquidity in the secondary market. These risks will vary depending upon the currency or currencies involved and will be more fully described in the applicable prospectus supplement.

DESCRIPTION OF WARRANTS

We may issue warrants for the purchase of shares of our common stock, shares of our preferred stock or debt securities. The following description sets forth certain general terms and provisions of the warrants that we may offer pursuant to this prospectus. The particular terms of the warrants and the extent, if any, to which the general terms and provisions may apply to the warrants so offered will be described in the applicable prospectus supplement.

Warrants may be issued independently or together with other securities and may be attached to or separate from any offered securities. Each series of warrants will be issued under a separate warrant agreement to be entered into between us and a bank or trust company, as warrant agent. The warrant agent will act solely as our agent in connection with the warrants and will not have any obligation or relationship of agency or trust for or with any holders or beneficial owners of warrants.

A copy of the forms of the warrant agreement and the warrant certificate relating to any particular issue of warrants will be filed with the SEC each time we issue warrants, and you should read those documents for provisions that may be important to you. For more information on how you can obtain copies of the forms of the warrant agreement and the related warrant certificate, see "Where You Can Find More Information."

Stock Warrants

The prospectus supplement relating to a particular issue of warrants to issue shares of our common stock or shares of our preferred stock will describe the terms of the common share warrants and preferred share warrants, including the following:

- the title of the warrants;
- the offering price for the warrants, if any;
- the aggregate number of the warrants;
- the designation and terms of the shares of common stock or shares of preferred stock that may be purchased upon exercise of the warrants;
- the terms for changes or adjustments to the exercise price of the warrants;
- if applicable, the designation and terms of the securities that the warrants are issued with and the number of warrants issued with each security;
- if applicable, the date from and after which the warrants and any securities issued with the warrants will be separately transferable;
- the number of shares of common stock or shares of preferred stock that may be purchased upon exercise of a warrant and the price at which the shares may be purchased upon exercise;
- the dates on which the right to exercise the warrants commence and expire;
- if applicable, the minimum or maximum amount of the warrants that may be exercised at any one time;
- the currency or currency units in which the offering price, if any, and the exercise price are payable;
- if applicable, a discussion of material United States federal income tax considerations;
- anti-dilution provisions of the warrants, if any;
- redemption or call provisions, if any, applicable to the warrants;
- any additional terms of the warrants, including terms, procedures and limitations relating to the exchange and exercise of the warrants; and
- any other information we think is important about the warrants.

Debt Warrants

The prospectus supplement relating to a particular issue of warrants to issue debt securities will describe the terms of those warrants, including the following:

- the title of the warrants;
- the offering price for the warrants, if any;
- the aggregate number of the warrants;
- the designation and terms of the debt securities purchasable upon exercise of the warrants;
- the terms for changes or adjustments to the exercise price of the warrants;
- if applicable, the designation and terms of the debt securities that the warrants are issued with and the number of warrants issued with each debt security;
- if applicable, the date from and after which the warrants and any debt securities issued with them will be separately transferable;
- the principal amount of debt securities that may be purchased upon exercise of a warrant and the price at which the debt securities may be purchased upon exercise;
- the dates on which the right to exercise the warrants will commence and expire;
- if applicable, the minimum or maximum amount of the warrants that may be exercised at any one time;
- whether the warrants represented by the warrant certificates or debt securities that may be issued upon exercise of the warrants will be issued in registered or bearer form;
- information relating to book-entry procedures, if any;
- the currency or currency units in which the offering price, if any, and the exercise price are payable;
- if applicable, a discussion of material United States federal income tax considerations;
- anti-dilution provisions of the warrants, if any;
- redemption or call provisions, if any, applicable to the warrants;
- any additional terms of the warrants, including terms, procedures and limitations relating to the exchange and exercise of the warrants; and
- any other information we think is important about the warrants.

Exercise of Warrants

Each warrant will entitle the holder of the warrant to purchase at the exercise price set forth in the applicable prospectus supplement the number of shares of common stock, shares of preferred stock or the principal amount of debt securities being offered. Holders may exercise warrants at any time up to the close of business on the expiration date set forth in the applicable prospectus supplement. After the close of business on the expiration date, unexercised warrants are void. Holders may exercise warrants as set forth in the prospectus supplement relating to the warrants being offered.

Until a holder exercises the warrants to purchase our shares of common stock, shares of preferred stock or debt securities, the holder will not have any rights as a holder of our shares of common stock, shares of preferred stock or debt securities, as the case may be, by virtue of ownership of warrants.

DESCRIPTION OF UNITS

We may issue, in one or more series, units consisting of common stock, preferred stock, or warrants for the purchase of common stock or preferred stock in any combination. We urge you to read the applicable prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the series of units being offered, as well as the complete unit agreement that contains the terms of the units. We will file as exhibits to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of unit agreement and any supplemental agreements that describe the terms of the series of units we are offering before the issuance of the related series of units.

Units may be issued under a unit agreement that we enter into with a unit agent. We will indicate the name and address of the unit agent, if applicable, in the prospectus supplement relating to the particular series of units being offered.

The applicable prospectus supplement may describe:

- the designation and terms of the units and of the securities composing the units, including whether and under what circumstances those securities may be held or transferred separately;
- any provisions for the issuance, payment, settlement, transfer or exchange of the units or of the securities composing the units; and
- whether the units will be issued in fully registered or global form.

SELLING STOCKHOLDERS

Selling stockholders are persons or entities that, directly or indirectly, have acquired or will from time to time acquire from us, our securities. If the registration statement of which this prospectus is a part is used by any selling stockholder for the resale of any shares of our common stock registered thereunder, information about such selling stockholder, its beneficial ownership of our securities and its relationship with us will be set forth in a supplement to this prospectus, or in one or more documents incorporated by reference into this prospectus or the applicable prospectus supplement. The applicable prospectus supplement will also disclose whether any of the selling stockholders has held any position or office with, has been employed by or otherwise has had a material relationship with us during the three years prior to the date of the applicable prospectus supplement.

PLAN OF DISTRIBUTION

We and any selling stockholder may sell our securities from time to time:

- to or through underwriters;
- through dealers;
- through agents;
- directly to one or more purchasers;
- ordinary brokerage transactions and transactions in which the broker-dealer solicits purchasers;
- block trades in which the broker-dealer will attempt to sell the shares as agent but may position and resell a portion of the block as principal to facilitate the transaction;
- in "at the market offerings," within the meaning of Rule 415(a)(4) of the Securities Act, to or through a market maker or into an existing trading market, on an exchange or otherwise;
- purchases by a broker-dealer as principal and resale by the broker-dealer for its account;
- an exchange distribution in accordance with the rules of the applicable exchange; or
- through a combination of any of these methods or any other method permitted by law.

We or selling stockholders may directly solicit offers to purchase securities, or agents may be designated to solicit such offers. In any applicable prospectus supplement relating to such offering, we will name any agent that could be viewed as an underwriter under the Securities Act and describe any commissions that we or selling stockholders must pay to any such agent. Any such agent will be acting on a best efforts basis for the period of its appointment or, if indicated in the applicable prospectus supplement, on a firm commitment basis. This prospectus may be used in connection with any offering of our securities through any of these methods or other methods described in the applicable prospectus supplement.

The distribution of our securities stock may be effected from time to time in one or more transactions:

- at a fixed price, or prices, which may be changed from time to time;
- at market prices prevailing at the time of sale;
- at prices related to such prevailing market prices; or
- at negotiated prices.

Each prospectus supplement will describe the method of distribution of the securities and any applicable restrictions.

A prospectus supplement or supplements (and any related free writing prospectus that we may authorize to be provided to you with respect to a particular offering) will describe the terms of the offering of our securities, including the following:

- the name or names of the agent or any underwriters;
- the name or names of the selling stockholders, if any;
- the public offering or purchase price of the securities or other consideration therefor, and the proceeds, if any, we will receive from the sale;
- any over-allotment options under which underwriters may purchase additional securities from us or any selling stockholders;
- any agency fees or underwriting discounts and commissions to be allowed or paid to the agent or underwriters;

- all other items constituting underwriting compensation;
- any discounts and commissions to be allowed or paid to dealers; and
- any securities exchange or market on which the securities will be listed.

If any underwriters or agents are used in the sale of our securities in respect of which this prospectus is delivered, we or selling stockholders will enter into an underwriting agreement, sales agreement or other agreement with them at the time of sale to them, and we will set forth in the applicable prospectus supplement relating to such offering the names of the underwriters or agents and the terms of the related agreement with them.

We may offer the securities, and selling stockholders may sell shares of our common stock, to the public through underwriting syndicates represented by managing underwriters or by underwriters without a syndicate. In connection with the offering of securities, we or selling stockholders may grant to the underwriters an option to purchase additional securities with an additional underwriting commission, as may be set forth in the applicable prospectus supplement.

If a dealer is used in the sale of the securities in respect of which the prospectus is delivered, we, a selling stockholders, or an underwriter will sell such securities to the dealer, as principal. The dealer, who may be deemed to be an "underwriter" as that term is defined in the Securities Act, may then resell such securities to the public at varying prices to be determined by such dealer at the time of resale.

We or selling stockholders may provide agents and underwriters with indemnification against civil liabilities, including liabilities under the Securities Act, or contribution with respect to payments that the agents or underwriters may make with respect to those liabilities.

Selling stockholders may be deemed to be underwriters under the Securities Act in connection with the common stock they resell and any profits on the sales may be deemed to be underwriting discounts and commissions under the Securities Act.

If so indicated in the applicable prospectus supplement, we or selling stockholders will authorize underwriters or other persons acting as agents to solicit offers by certain institutions to purchase securities from us or selling stockholders pursuant to delayed delivery contracts providing for payment and delivery on the date stated in the applicable prospectus supplement. Each contract will be for an amount not less than, and the aggregate amount of securities sold pursuant to such contracts shall not be less nor more than, the respective amounts stated in the applicable prospectus supplement. Institutions with whom the contracts, when authorized, may be made include commercial and savings banks, insurance companies, pension funds, investment companies, educational and charitable institutions and other institutions. Delayed delivery contracts will not be subject to any conditions except that:

- the purchase by an institution of the securities covered under that contract shall not at the time of delivery be prohibited under the laws of the jurisdiction to which that institution is subject; and
- if the securities are also being sold to underwriters acting as principals for their own account, the underwriters shall have purchased such securities not sold for delayed delivery.

Offered securities may also be offered and sold, if so indicated in the applicable prospectus supplement, in connection with a remarketing upon their purchase, in accordance with a redemption or repayment pursuant to their terms, or otherwise, by one or more remarketing firms, acting as

principals for their own accounts or as agents for us. Any remarketing firm will be identified and the terms of its agreement, if any, with us and its compensation will be described in the applicable prospectus supplement. Remarketing firms may be deemed to be underwriters in connection with their remarketing of offered securities.

Certain agents, underwriters and dealers, and their associates and affiliates, may be customers of, have borrowing relationships with, engage in other transactions with, or perform services, including investment banking services, for us or selling stockholders or one or more of our respective affiliates in the ordinary course of business for which they receive compensation.

In order to facilitate the offering of our securities, any underwriters may engage in transactions that stabilize, maintain or otherwise affect the price of the securities or any other securities the prices of which may be used to determine payments on such securities. Specifically, any underwriters may overallot in connection with the offering, creating a short position for their own accounts. In addition, to cover overallotments or to stabilize the price of the securities or of any such other securities, the underwriters may bid for, and purchase, the securities or any such other securities in the open market. Finally, in any offering of our securities through a syndicate of underwriters, the underwriting syndicate may reclaim selling concessions allowed to an underwriter or a dealer for distributing the securities in the offering if the syndicate repurchases previously distributed securities in transactions to cover syndicate short positions, in stabilization transactions or otherwise. Any of these activities may stabilize or maintain the market price of the securities above independent market levels. Any such underwriters are not required to engage in these activities and may end any of these activities at any time.

We may engage in at the market offerings into an existing trading market in accordance with Rule 415(a)(4) under the Securities Act. In addition, we may enter into derivative transactions with third parties, or sell securities not covered by this prospectus to third parties in privately negotiated transactions. If the applicable prospectus supplement so indicates, in connection with those derivatives, the third parties may sell securities covered by this prospectus and the applicable prospectus supplement, including in short sale transactions. If so, the third party may use securities pledged by us or borrowed from us or others to settle those sales or to close out any related open borrowings of stock, and may use securities received in settlement of those derivatives to close out any related open borrowings of stock. The third party in such sale transactions will be an underwriter and, if not identified in this prospectus, will be named in the applicable prospectus supplement (or a post-effective amendment). In addition, we may otherwise loan or pledge securities to a financial institution or other third party that in turn may sell the securities short using this prospectus and an applicable prospectus supplement. Such financial institution or other third party may transfer its economic short position to investors in our securities or in connection with a concurrent offering of other securities.

Under Rule 15c6-1 of the Exchange Act, trades in the secondary market generally are required to settle in two business days, unless the parties to any such trade expressly agree otherwise. The applicable prospectus supplement may provide that the original issue date for your securities may be more than two scheduled business days after the trade date for your securities. Accordingly, in such a case, if you wish to trade securities on any date prior to the second business day before the original issue date for your securities, you will be required, by virtue of the fact that your securities initially are expected to settle in more than two scheduled business days after the trade date for your securities, to make alternative settlement arrangements to prevent a failed settlement.

In compliance with the guidelines of the Financial Industry Regulatory Authority, Inc., or FINRA, the aggregate maximum discount, commission or agency fees or other items constituting

underwriting compensation to be received by any FINRA member or independent broker-dealer will not exceed 8% of the proceeds from any offering pursuant to this prospectus and any applicable prospectus supplement.

The specific terms of any lock-up provisions in respect of any given offering will be described in the applicable prospectus supplement.

The anticipated date of delivery of offered securities will be set forth in the applicable prospectus supplement relating to each offer.

LEGAL MATTERS

Certain legal matters, including the validity of the issuance of the securities offered, will be passed upon for us by Morgan, Lewis & Bockius LLP, Boston, Massachusetts.

EXPERTS

The consolidated financial statements of Rhythm Pharmaceuticals, Inc. appearing in Rhythm Pharmaceutical's Current Report on Form 8-K dated November 9, 2018 have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon included therein, and incorporated herein by reference. Such financial statements are, and audited financial statements to be included in subsequently filed documents will be, incorporated herein in reliance upon the report of Ernst & Young LLP pertaining to such financial statements to the extent covered by consents filed with the Securities and Exchange Commission given on the authority of such firm as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We are subject to the information requirements of the Exchange Act, and in accordance with the Exchange Act, file annual, quarterly and special reports, proxy statements and other information with the SEC. These documents also may be accessed through the SEC's electronic data gathering, analysis and retrieval system, or EDGAR, via electronic means, including the SEC's home page on the Internet (www.sec.gov). Our corporate website address is *www.rhythmtx.com*. Information contained on or accessible through our website is not a part of this prospectus, and the inclusion of our website address in this prospectus is an inactive textual reference only.

This prospectus is part of the registration statement on Form S-3 we filed with the SEC under the Securities Act and does not contain all the information set forth in the registration statement. Whenever a reference is made in this prospectus to any of our contracts, agreements or other documents, the reference may not be complete and you should refer to the exhibits that are a part of the registration statement or the exhibits to the reports or other documents incorporated by reference into this prospectus for a copy of such contract, agreement or other document.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to incorporate by reference into this prospectus the information contained in documents that we file with them, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus. Information in this prospectus supersedes information incorporated by reference that we filed with the SEC before the date of this prospectus, while information that we file later with the SEC will automatically update and supersede prior information. Any information so updated and superseded shall not be deemed, except as so updated and superseded, to constitute a part of this prospectus. We incorporate by reference the documents listed below and any future filings we will make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, prior to the termination of the offering. Notwithstanding the foregoing, unless specifically stated to the contrary, none of the information that is not deemed "filed" with the SEC, including information furnished under Items 2.02 or 7.01 of any Current Report on Form 8-K, will be incorporated by reference into, or otherwise included in, this prospectus:

1. our annual report on Form 10-K for the fiscal year ended December 31, 2017 filed with the SEC on March 12, 2018 (the "Form 10-K");
2. the information contained in our definitive proxy statement on Schedule 14A for our 2018 annual meeting of stockholders filed with the SEC on April 30, 2018, to the extent incorporated by reference in Part III of the Form 10-K;
3. our quarterly reports on Form 10-Q for the quarters ended March 31, 2018, June 30, 2018 and September 30, 2018, filed with the SEC on May 14, 2018, August 8, 2018 and November 9, 2018, respectively;
4. our current reports on Form 8-K filed with the SEC on March 12, 2018 (not including any information furnished under Item 2.02 or 9.01 of such Form 8-K or any other information that is identified as "furnished" rather than filed, which information is not incorporated by reference herein), April 2, 2018, June 11, 2018, August 9, 2018 and November 9, 2018; and
5. our description of our common stock contained in the registration statement on Form 8-A, filed on September 29, 2017, and all amendments and reports updating such description.

We make available, free of charge, through our website our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. You may also obtain, free of charge, a copy of any of these documents (other than exhibits to these documents unless the exhibits are specifically incorporated by reference into these documents or referred to in this prospectus) by writing or calling us at the following address and telephone number:

Rhythm Pharmaceuticals, Inc.
500 Boylston Street
11th Floor
Boston, Massachusetts 02116
(857) 264-4280

You should rely only on the information incorporated by reference or provided in this prospectus or any prospectus supplement. We have not authorized anyone to provide you with different information. We are not making an offer of these securities in any state where the offer is not permitted. You should not assume that the information in this prospectus or in the documents incorporated by reference is accurate as of any date other than the date on the front of this prospectus or those documents.

Table of Contents

$150,000,000

RHYTHM PHARMACEUTICALS, INC.

Common Stock

PROSPECTUS SUPPLEMENT

MORGAN STANLEY *GOLDMAN SACHS & CO. LLC* *COWEN*

NEEDHAM & COMPANY

October , 2019