

PROSPECTUS SUPPLEMENT
(To Prospectus dated November 9, 2018)



5,000,000 Shares

RHYTHM PHARMACEUTICALS, INC.

Common Stock

We are offering 5,000,000 shares of our common stock.

Our common stock is listed on The Nasdaq Global Market under the symbol "RYTM." On February 3, 2021, the last reported sale price for our common stock on The Nasdaq Global Market was \$31.44 per share.

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-8](#) of this prospectus supplement.

| | <u>Per Share</u> | <u>Total</u> |
|---|------------------|----------------|
| Public offering price | \$ 30.00 | \$ 150,000,000 |
| Underwriting discounts and commissions ⁽¹⁾ | \$ 1.80 | \$ 9,000,000 |
| Proceeds to us, before expenses | \$ 28.20 | \$ 141,000,000 |

(1) We have also agreed to reimburse the underwriters for certain of their expenses. See "Underwriters" beginning on page [S-20](#) of this prospectus supplement for more information about these arrangements.

We have granted the underwriters the right to purchase up to an aggregate of 750,000 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 February 9, 2021.

MORGAN STANLEY BofA SECURITIES COWEN STIFEL

CANACCORD GENUITY

The date of this prospectus supplement is February 4, 2021.

TABLE OF CONTENTS

Prospectus Supplement

| | Page |
|---|----------------------|
| ABOUT THIS PROSPECTUS SUPPLEMENT | S-1 |
| CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS | S-2 |
| PROSPECTUS SUPPLEMENT SUMMARY | S-3 |
| THE OFFERING | S-7 |
| RISK FACTORS | S-8 |
| USE OF PROCEEDS | S-13 |
| DIVIDEND POLICY | S-14 |
| DILUTION | S-15 |
| MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES TO NON-U.S. HOLDERS | S-16 |
| UNDERWRITING | S-20 |
| LEGAL MATTERS | S-28 |
| EXPERTS | S-28 |
| WHERE YOU CAN FIND MORE INFORMATION | S-29 |
| INCORPORATION OF CERTAIN INFORMATION BY REFERENCE | S-29 |

Prospectus

| | Page |
|---|--------------------|
| ABOUT THIS PROSPECTUS | ii |
| PROSPECTUS SUMMARY | 1 |
| RISK FACTORS | 3 |
| CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING STATEMENTS | 3 |
| USE OF PROCEEDS | 5 |
| THE SECURITIES WE MAY OFFER | 5 |
| DESCRIPTION OF CAPITAL STOCK | 6 |
| DESCRIPTION OF DEBT SECURITIES | 12 |
| DESCRIPTION OF WARRANTS | 20 |
| DESCRIPTION OF UNITS | 22 |
| SELLING STOCKHOLDERS | 22 |
| PLAN OF DISTRIBUTION | 23 |
| LEGAL MATTERS | 26 |
| EXPERTS | 26 |
| WHERE YOU CAN FIND MORE INFORMATION | 26 |
| INCORPORATION OF CERTAIN INFORMATION BY REFERENCE | 27 |

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 this prospectus supplement. 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 or any free writing prospectus. If any statement in one of these documents is inconsistent with a statement in another document having a later date—for example, a document incorporated by reference in this prospectus supplement—the statement in the document having the later date modifies or supersedes the earlier statement.

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, including the common stock that we are offering under this prospectus supplement and the accompanying prospectus. 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 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 share. 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 this prospectus supplement and the other documents we file with SEC. Accordingly, investors should not place undue reliance on this information.

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.

This prospectus supplement may include trademarks, tradenames and service marks that are the property of us or other organizations. Solely for convenience, trademarks and tradenames referred to in this prospectus supplement may appear without the ® and ™ symbols, but those references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights or that the applicable owner will not assert its rights, to these trademarks and tradenames.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein and any free writing prospectus that we have authorized for use in connection with this offering may contain forward-looking statements. All statements other than statements of historical facts contained in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein and any free writing prospectus, including, without limitation, statements regarding the marketing and commercialization of IMCIVREE (setmelanotide); the success, cost and timing of our product development activities and clinical trials; our financial performance, including our expectations regarding our existing cash, operating losses, expenses and sources of future financing; our ability to hire and retain necessary personnel; patient enrollments and the timing thereof; the timing of announcements regarding results of clinical trials; our ability to protect our intellectual property; our ability to negotiate our collaboration agreements, if needed; our marketing, commercial sales, and revenue generation; expectations surrounding our manufacturing arrangements; the impact of the novel coronavirus, or COVID-19, pandemic on our business and operations and our future financial results; ceasing to qualify as an emerging growth company or a smaller reporting company as of December 31, 2020; and our use of the proceeds from this offering are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. This prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein and any free writing prospectus may also contain estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

In some cases, you can identify forward-looking statements by terms such as “may,” “will,” “should,” “expect,” “plan,” “anticipate,” “could,” “intend,” “target,” “project,” “contemplates,” “believes,” “estimates,” “predicts,” “potential” or “continue” or the negative of these terms or other similar expressions. The forward-looking statements in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein and any free writing prospectus are only predictions. We have based these forward-looking statements largely on our current expectations and projections about future events and financial trends that we believe may affect our business, financial condition and results of operations. These forward-looking statements speak only as of the respective dates of this prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein and any free writing prospectus, as applicable, and are subject to a number of risks, uncertainties and assumptions, including those described in this prospectus supplement and the other documents we file with SEC and incorporated by reference herein. The events and circumstances reflected in our forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements. Moreover, we operate in an evolving environment. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein and any free writing prospectus, whether as a result of any new information, future events, changed circumstances or otherwise.

PROSPECTUS SUPPLEMENT SUMMARY

This summary provides a general overview of selected information and does not contain all of the information you should consider before buying shares of our common stock. Therefore, you should read this entire prospectus supplement, the accompanying prospectus and any free writing prospectus that we have authorized for use in connection with this offering carefully, including the information incorporated by reference, before deciding to invest in our common stock. You should carefully consider the information set forth under “Risk Factors” beginning on page [S-8](#) of this prospectus supplement and incorporated by reference to our Annual Report on Form 10-K and our quarterly reports on Form 10-Q.

Our Company

We are a commercial-stage biopharmaceutical company focused on the development and commercialization of therapeutics for the treatment of rare genetic diseases which are characterized by early-onset, severe obesity and an insatiable hunger, or hyperphagia. Our lead product candidate is IMCIVREE (setmelanotide), a potent melanocortin-4 receptor, or MC4R, agonist for the treatment of rare genetic diseases of obesity. We believe IMCIVREE, for which we have exclusive worldwide rights, has the potential to restore dysfunctional MC4R signaling due to impaired MC4R pathway function. 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. IMCIVREE has been approved by the U.S. Food and Drug Administration, or FDA, for chronic weight management in adult and pediatric patients six years of age and older with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency confirmed by genetic testing. We expect IMCIVREE to be commercially available in the first quarter of 2021.

Recent Developments

Phase 2 Basket Study

On January 26, 2021, we announced new proof-of-concept interim data from our ongoing Phase 2 Basket Study across individuals with one of three distinct rare genetic diseases of obesity: HET obesity due to a genetic variant in one of the two alleles of the *POMC*, *PCSK1* or *LEPR* gene, or HETs; obesity due to *SRC1* deficiency; and obesity due to *SH2B1* deficiency. Across five cohorts, 65 patients with severe obesity were eligible for analysis as of a cutoff date of December 17, 2020. Twelve of these patients had failed bariatric surgery. The primary endpoint of the study is the percent of patients in each subgroup showing at least a 5 percent loss of body weight over three months.

HET obesity (*POMC*, *PCSK1*, *LEPR*) highlights include, as of the cutoff date:

- Overall, 12 of 35 patients (34.3 percent) achieved the primary endpoint; this full analysis includes six patients who withdrew early;
- Mean reduction from baseline in body weight across all 35 patients was -3.7 percent, which includes both clinical responders and non-responders;
- Among the 12 patients who achieved the primary endpoint (responder group), the mean reduction from baseline in body weight was -10.1 percent;
- Patients with HET obesity were stratified into three pre-specified cohorts by classification of their genetic variants according to American College of Medical Genetics guidelines:
 - Four of eight patients (50.0 percent) with a pathogenic or likely pathogenic variant achieved greater than 5 percent weight loss;
 - Four of eight patients (50.0 percent) with the N221D variant of the *PCSK1* gene achieved greater than 5 percent weight loss;
 - Four of 19 patients (21.1 percent) with a variant of unknown significance achieved greater than 5 percent weight loss.

Data from the *SRC1* and *SH2B1* cohorts were based on an interim analysis of patients who completed 12 weeks of therapy. This analysis did not include 15 patients who withdrew early due to COVID-related issues,

adverse events or were lost to follow-up. Also not included were data from 12 patients who remain ongoing but have not yet reached 12 weeks of therapy. A majority of the patients who withdrew early experienced weight loss.

Obesity due to *SRC1* deficiency highlights include, as of the cutoff date:

- Four of 13 patients (30.8 percent) achieved the primary endpoint;
- Mean reduction from baseline in body weight across all 13 patients was -3.7 percent, which included both clinical responders and non-responders;
- Among the four patients who achieved the primary endpoint (responder group) the mean reduction from baseline in body weight was -8.4 percent.

Obesity due to *SH2B1* deficiency highlights include, as of the cutoff date:

- Nine of 17 patients (52.9 percent) achieved greater than 5 percent weight loss over 12 weeks of therapy;
- Mean reduction from baseline in body weight across all 17 patients was -3.9 percent, which included clinical responders and non-responders;
- Among the nine patients who achieved the primary endpoint (responder group), the mean reduction from baseline in body weight was -7.1 percent.

Consistent with prior clinical experience, setmelanotide was generally well tolerated in each of these rare genetic diseases of obesity. The most common treatment-emergent adverse events included mild injection site reactions, hyperpigmentation, and nausea and vomiting, which occurred early in the treatment course. There were no serious adverse events related to treatment with setmelanotide.

We are in discussions with the FDA to define a potential path for setmelanotide towards registration for these indications. Pending the outcome of these discussions, we plan to initiate a pivotal Phase 3 trial evaluating setmelanotide in patients with HET obesity and *SRC1* and *SH2B1* deficiency obesities in the second half of 2021.

Pivotal Phase 3 Clinical Trial in Bardet-Biedl Syndrome and Alström Syndrome

In December 2020, we announced positive topline results from a pivotal Phase 3 clinical trial evaluating setmelanotide for the treatment of insatiable hunger and severe obesity in individuals with Bardet-Biedl syndrome, or BBS, or Alström syndrome. The trial met its primary and all key secondary endpoints, showing statistically significant and clinically meaningful reductions in weight and hunger scores. All primary endpoint responders were patients with BBS. There were three evaluable patients with Alström syndrome and none of them met the primary endpoint.

Thirty-two individuals with BBS and six individuals with Alström syndrome were enrolled in the pivotal cohort for this Phase 3 trial. The primary analysis was conducted on 31 evaluable participants (28 with BBS and three with Alström syndrome) 12 years old and older. Five study participants (three with BBS and two with Alström syndrome) were younger than 12 years old at enrollment.

Eleven of 31, or 34.5 percent, of participants achieved the primary endpoint of at least 10 percent reduction in body weight from baseline at approximately 52 weeks of therapy ($p=0.0024$). Eleven of 28 patients with BBS achieved 10 percent reduction in body weight and no patients with Alström syndrome achieved 10 percent reduction in body weight.

Key secondary endpoints included additional weight loss and hunger reduction analyses. Mean reduction from baseline in body weight was -6.2 percent ($p<0.0001$). Mean reduction from baseline in most hunger rating was -30.8 percent ($p<0.0001$) and 60.2 percent of participants achieved at least 25 percent reduction in most hunger scores from baseline at approximately 52 weeks of therapy ($p<0.0001$).

Consistent with prior clinical experience, setmelanotide was observed to be generally well tolerated. Treatment-emergent adverse events included mild injection site reactions and nausea with infrequent vomiting. There were no serious adverse events related to treatment with setmelanotide. Eight patients discontinued from

study drug treatment during the trial, five due to adverse events (one on placebo at the time), and three for other reasons (one on placebo at the time).

We plan to complete regulatory submissions to both the FDA and the European Medicines Association for BBS in the second half of 2021. We expect to determine the next steps for Alström syndrome upon completing a full analysis of the final data from this trial in the first half of 2021. We anticipate sharing the full data from this Phase 3 clinical trial in a forthcoming publication or in a presentation at an upcoming medical meeting.

BMI-Z Data from Phase 3 Clinical Trials

On January 26, 2021, we presented new, predefined, exploratory endpoint data from our Phase 3 clinical trial in patients with BBS and AS, showing the results of setmelanotide on BMI-Z scores for patients younger than 18 years old with BBS. The BMI-Z score, or BMI standard deviation score, represents the number of standard deviations from median BMI by child age and sex, and measures relative weight adjusted for a child's age and sex.

In 16 patients younger than 18 with BBS, setmelanotide was associated with statistically significant and clinically meaningful reductions in BMI-Z scores. In these patients, the mean BMI-Z score was reduced from 3.74 at baseline to 2.98 for a reduction of -0.76, or -24.5 percent ($p=0.0006$).

We had also evaluated BMI Z-scores in our previous pivotal trials as a predefined, exploratory endpoint. In six patients younger than 19 with *POMC* deficiency obesity, the mean BMI-Z score was reduced from 3.35 at baseline to 1.73 for a reduction of -1.6, or -49.2% ($p=0.007$). In three patients younger than 19 with *LEPR* deficiency obesity, the mean BMI-Z score was reduced from 3.52 at baseline to 3.03 for a reduction of -0.49, or -13.4% ($p=0.012$).

Updated U.S. Prevalence Estimates for Basket Study Indications

We have increased our internal database of sequencing samples to approximately 37,500. We are using these data to support our research, patient finding and community building efforts in order to better understand rare genetic diseases of obesity. Our genetic sequencing results demonstrated that approximately 10 to 15 percent of obese individuals sampled as of September 30, 2020, showed a relevant MC4R pathway genotype in the *POMC*, *PCSK1*, and *LEPR* HETs and *SRC1* or *SH2B1* genes. We estimate, based on a combination of these sequencing yields, as well as clinical data on setmelanotide response rates among patients with variants in these genes, that there are 100,000 to 200,000 potentially setmelanotide-responsive patients in the United States.

Exploratory Basket Study in an Additional 31 MC4R Pathway Genes

On January 26, 2021, we presented new data generated from our proprietary gene curation and selection strategy, which is designed to evaluate a gene's relevance to the MC4R pathway with the goal of identifying genetic patient populations with the potential to benefit from setmelanotide therapy. Using this proprietary approach, we identified an additional 31 MC4R pathway genes with strong or very strong pathway relevance. Pending discussions with the FDA, we plan to initiate a new exploratory MC4R pathway basket trial in patients with these 31 new genes in the second half of 2021.

Other Clinical Updates

In the first half of 2021, we plan to initiate a Phase 2 clinical trial in hypothalamic obesity, initiate a potentially registrational clinical trial of the weekly formulation of setmelanotide, and announce data from a Phase 2 basket study in MC4R-recusable patients. In the second half of 2021, we plan to initiate a clinical trial of setmelanotide in pediatric patients aged two to six and expect to receive a decision from the EMA on our MAA for setmelanotide to treat individuals living with *POMC* or *LEPR* deficiency obesities.

PRV Transfer

On January 5, 2021, we entered into an asset purchase agreement with Alexion Pharmaceuticals, Inc., or Alexion, pursuant to which we agreed to sell our Rare Pediatric Disease Priority Review Voucher, PRV, to Alexion, or the PRV Transfer. We were awarded the voucher under a FDA program intended to encourage the

development of certain rare pediatric disease product applications. We received the PRV when IMCIVREE was approved by the FDA. Pursuant to the transfer agreement, Alexion agreed to pay us \$100 million in cash upon the closing of the sale. The transaction remains subject to customary closing conditions, including the expiration or termination of the applicable waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976.

Preliminary Financial Information

Our audited financial statements for the year ended December 31, 2020 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 \$173.0 million of cash, cash equivalents and short-term investments as of December 31, 2020. Based on our current plans, we believe our existing cash, cash equivalents and short term-investments and the expected proceeds from the PRV Transfer will be sufficient to fund our operations into the second half of 2022.

We have not yet completed our financial close process for the year ended December 31, 2020. This estimate of our cash, cash equivalents and short-term investments as of December 31, 2020 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 December 31, 2020 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 results will be included in our Annual Report on Form 10-K for the year ended December 31, 2020.

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, 12th 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 supplement, and the inclusion of our website address in this prospectus supplement is an inactive textual reference only.

THE OFFERING

| | |
|--|---|
| Common stock offered by us | 5,000,000 shares of our common stock |
| Common stock to be outstanding after this offering | 49,235,903 shares (or 49,985,903 shares if the underwriters exercise their option to purchase additional shares in full) |
| Option to purchase additional common stock offered by us | Up to 750,000 additional shares of our common stock |
| Use of Proceeds | We estimate that our net proceeds from this offering will be approximately \$140.4 million, or approximately \$161.6 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 to advance the clinical development of setmelanotide in other MC4R pathway indications, for disease-education and community-building activities, patient identification, pre-commercialization activities for setmelanotide in BBS, commercialization activities related to IMCIVREE and for working capital and general corporate purposes. |
| Risk Factors | You should read the “Risk Factors” section beginning on page S-8 of this prospectus supplement and the other information included in, or incorporated by reference into, this prospectus supplement for a discussion of certain factors you should carefully consider before deciding to invest in our common stock. |
| Nasdaq Global Market Symbol | “RYTM” |
| <p>The number of shares of our common stock to be outstanding after this offering is based on 44,235,903 shares outstanding as of December 31, 2020 and excludes:</p> <ul style="list-style-type: none"> • 5,199,235 shares of common stock issuable upon the exercise of stock options outstanding as of December 31, 2020, at a weighted average exercise price of \$21.30 per share; • 2,108,764 shares of common stock reserved for future issuance under our 2017 equity incentive plan, or the 2017 Plan, as of December 31, 2020; • 1,000,993 shares of common stock reserved for future issuance under our 2017 employee stock purchase plan, or the ESPP, as of December 31, 2020; and • 176,537 shares of common stock issuable upon the vesting of restricted stock units outstanding as of December 31, 2020. <p>Unless otherwise indicated, this prospectus supplement reflects and assumes the following:</p> <ul style="list-style-type: none"> • no exercise of the outstanding options or vesting of the restricted stock units described above; and • no exercise by the underwriters of their option to purchase additional shares of common stock. | |

RISK FACTORS

Investment in any securities offered pursuant to this prospectus supplement and the accompanying prospectus involves risks. You should carefully consider the risk factors described below and in our [Quarterly Report on Form 10-Q for the quarterly period ended September 30, 2020](#) incorporated by reference in this prospectus supplement, any amendment or update thereto reflected in subsequent filings with the SEC, including in our Annual Reports on Form 10-K and Quarterly Reports on Form 10-Q, and all other information contained or incorporated by reference in this prospectus supplement, as updated by our subsequent filings under the Exchange Act. The occurrence of any of these risks might cause you to lose all or part of your investment in the offered securities.

Risks Related to the Development 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 approximately 37,500 patients, as of September 30, 2020, 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 multiple epidemiological methods, we have estimated the potential addressable patient populations with these MC4R pathway deficiencies based on the following sources and assumptions:

- ***POMC Deficiency Obesity.*** POMC Deficiency Obesity is defined by the presence of biallelic variants in the POMC or PCSK1 genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VOUS). 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/m²) 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 PCSK1 gene disorders), defined as patients having biallelic variants in the POMC or PCSK1 genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VOUS), of approximately 0.05%.
- ***LEPR Deficiency Obesity.*** LEPR Deficiency Obesity is defined by the presence of biallelic variants in the LEPR gene that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VOUS). 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 CDC prevalence numbers for severe adult obese patients (BMI, greater than 40 kg/m²) 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, defined as patients having biallelic variants in the LEPR gene that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VOUS), of approximately 0.09%.
- *Bardet-Biedl Syndrome*. Our addressable patient population estimate for BBS is approximately 1,500 to 2,500 patients in the United States based on:
 - published prevalence estimates of one in 100,000 in North America, which projects to approximately 3,250 people in the United States. We believe the majority of these patients are addressable patients; and
 - our belief that with wider availability of genetic testing expected for BBS and increased awareness of new treatments, the number of patients diagnosed with this disorder will increase.
 - *Alström Syndrome*. Our addressable patient population estimate for Alström syndrome is approximately 1,000 patients worldwide and approximately 500 patients in the United States. This estimate is based on:
 - published prevalence estimates of one in 1,000,000 in North America, which projects to approximately 325 people in the United States. We believe the majority of these patients are addressable patients; and
 - our belief that with wider availability of genetic testing expected for Alström syndrome and increased awareness of new treatments, the number of patients diagnosed with this disorder will increase.
 - *POMC, PCSK1, or LEPR Heterozygous Deficiency Obesities; SRC1 and SH2B1 Deficiency Obesities*. Our potential setmelanotide-responsive patient population estimate for POMC, PCSK1, or LEPR heterozygous, SRC1 and SH2B1 deficiency obesity patients with at least one variant interpreted as pathogenic, likely pathogenic, or of uncertain significance (VOUS) is 100,000 to 200,000 patients in the United States. Our estimates are based on:
 - U.S. Census Bureau figures for adults and children and CDC prevalence numbers for severe adult obese patients (BMI greater than 40 kg/m²) and for severe early onset obese children (99th percentile at ages two to 17 years old);
 - our internal sequencing yield of patients with POMC, PCSK1, or LEPR heterozygous, SRC1 or SH2B1 variants interpreted as pathogenic, likely pathogenic, or of uncertain significance (VOUS) of approximately 10-15%; and
 - a clinical response rate of 40% for patients carrying pathogenic or likely pathogenic variants, and 20% for patients carrying a variant of uncertain significance (VOUS).

The clinical response rate used in this calculation is based on the clinical data currently available to us from our trials and may change as more data become available.

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

- U.S. Census Bureau figures for adults and children and CDC prevalence numbers for severe adult obese patients (BMI, greater than 40 kg/m²) and for severe early onset obese children (99th percentile at ages two to 17 years old); and
- our internal sequencing yield for MC4R deficiency obesity patients of approximately 2.0% prior to application of functional filters.
- *Smith-Magenis Syndrome.* Our addressable patient population estimate for Smith-Magenis syndrome is approximately greater than 2,400 patients in the United States. This estimate is based on:
 - published prevalence estimates of one in 25,000 in the United States, which projects to approximately 13,000 people in the United States;
 - published prevalence estimates that approximately 10% of patients with Smith-Magenis syndrome have RAI1 variants that may affect the MC4R pathway and 90% of patients with Smith-Magenis syndrome have 17p11.2 chromosomal deletions which also may affect the MC4R pathway, of which approximately 67% and 13%, respectively, live with obesity; and
 - U.S. Census Bureau figures for total population of adults and children.

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

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 clearance, approval or CE marking of an in vitro companion diagnostic device to ensure appropriate selection of patients as a condition of approving setmelanotide in additional indications. The requirement that we obtain clearance, approval or CE mark of an in vitro companion diagnostic device will require substantial financial resources, and could delay or prevent the receipt of additional regulatory approvals for setmelanotide, or adversely affect those we have already obtained.

We have focused our development of setmelanotide as a treatment for obesity caused by certain genetic deficiencies affecting the MC4R pathway. To date, we have employed *in vitro* genetic diagnostic testing to select patients for enrollment in our clinical trials, including our clinical trials for IMCIVREE and for other potential indications for setmelanotide. If the safe and effective use of any of our product candidates depends on an *in vitro* diagnostic that is not otherwise commercially available, then the FDA may require approval or clearance of that diagnostic, known as a companion diagnostic, at the same time as, or in connection with, the FDA approval of such product candidates.

If the FDA or a comparable regulatory authority requires clearance or approval of a companion diagnostic for setmelanotide, 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 us from obtaining additional approvals for setmelanotide, or adversely affect the approvals we have already obtained. For example, in November 2020, FDA approved IMCIVREE for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to POMC, PCSK1, or LEPR deficiencies confirmed by genetic testing demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance. Although the FDA did not require that we obtain approval of a companion diagnostic prior to approving the New Drug Application, or NDA, for IMCIVREE, in connection with the NDA approval we agreed as a post-marketing commitment to conduct adequate analytical and clinical validation testing to develop and establish an *in-vitro* companion diagnostic device to accurately and reliably detect patients with variants in the POMC, PCSK1, and LEPR genes that

may benefit from setmelanotide therapy. In September 2020, our collaboration partner, Prevention Genetics, submitted a de novo request seeking FDA authorization to market such an *in-vitro* companion diagnostic device for IMCIVREE as a Class II medical device. In December 2020, the FDA sent Prevention Genetics a major deficiency letter in response to the de novo request, which among other things, placed the review on hold and requested additional information needed to support the requested device classification. Although we believe that Prevention Genetics will be able to resolve the issues identified in the major deficiency letter, they may be unsuccessful in doing so, and Prevention Genetics may be required to submit and obtain approval of a PMA application for the *in-vitro* companion diagnostic device before we are able to fulfill our post-marketing commitment to FDA, which would lead to further delay and could entail significant additional expense. If we are unable to fulfill our postmarket commitments for IMCIVREE in a timely manner, the FDA could take enforcement action against us, which could adversely affect our prospects. Further, if the FDA or a comparable regulatory authority requires clearance or approval of a companion diagnostic when we seek additional approvals for setmelanotide, 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 us from obtaining such additional approvals for setmelanotide, or adversely affect the approvals we have already obtained.

Risks Related to this Offering

If you purchase shares of our common stock sold in this offering, you will experience immediate and substantial dilution in the net tangible book value of your shares of common stock. In addition, we may issue additional equity or convertible debt securities in the future, which may result in additional dilution to you.

The price per share of our common stock being offered may be higher than the net tangible book value per share of our outstanding common stock prior to this offering. The sale of 5,000,000 shares of common stock after deducting underwriting commissions and discounts and estimated offering expenses payable by us will result in new investors in this offering incurring immediate dilution of \$23.14 per share of common stock as of September 30, 2020. For a more detailed discussion of the foregoing, see the section entitled “Dilution” below. To the extent outstanding stock options are exercised or restricted stock units vest, there will be further dilution to new investors. In addition, to the extent we need to raise additional capital in the future and we issue additional shares of common stock or securities convertible or exchangeable for our shares of common stock, our then existing shareholders may experience dilution and the new securities may have rights senior to those of our shares of common stock offered in this offering.

We have broad discretion in the use of the net proceeds from this offering and may not use them effectively.

Our management will have broad discretion in the application of the net proceeds from this offering, including for any of the purposes described in the section entitled “Use of Proceeds,” and you will not have the opportunity as part of your investment decision to assess whether the net proceeds are being used appropriately. Because of the number and variability of factors that will determine our use of the net proceeds from this offering, their ultimate use may vary substantially from their currently intended use. Our management might not apply our net proceeds in ways that ultimately increase the value of your investment. We intend to use the net proceeds from this offering to advance the clinical development of setmelanotide in other MC4R pathway indications, for disease-education and community-building activities, patient identification, pre-commercialization activities for setmelanotide in BBS, commercialization activities related to IMCIVREE and for working capital and general corporate purposes. See the section entitled “Use of Proceeds” on page S-13 of this prospectus supplement. The failure by our management to apply these funds effectively could harm our business. Pending their use, we plan to invest the net proceeds from this offering in short- and intermediate-term, interest-bearing obligations, investment-grade instruments, certificates of deposit or direct or guaranteed obligations of the U.S. government. These investments may not yield a favorable return to our shareholders. If we do not invest or apply the net proceeds from this offering in ways that enhance shareholder value, we may fail to achieve expected financial results, which could cause our share price to decline.

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 shareholders.

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 that 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, our directors and certain shareholders affiliated with our directors have agreed that, subject to certain exceptions, during the period ending 90 days in the case of us and our executive officers and 30 days in the case of our directors and their affiliated shareholders, 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 Morgan Stanley & Co. LLC, BofA Securities, Inc. and Cowen and Company, LLC, 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.”

USE OF PROCEEDS

We estimate that the net proceeds from this offering will be approximately \$140.4 million (or approximately \$161.6 million if the underwriters exercise their option to purchase additional shares in full), after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

We intend to use the net proceeds from this offering to advance the clinical development of setmelanotide in other MC4R pathway indications, for disease-education and community-building activities, patient identification, pre-commercialization activities for setmelanotide in BBS, commercialization activities related to IMCIVREE and for working capital and general corporate purposes.

Based on our current plans, we believe our cash and cash equivalents and short-term investments, together with the expected proceeds from the PRV Transfer and 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 second half of 2023. We have not determined the amounts we plan to spend in any of the areas identified above or the timing of these expenditures. As a result, our management will have broad discretion to allocate the net proceeds to us from this offering, and investors will be relying on the judgment of our management regarding the application of the proceeds from this offering. We reserve the right to change the use of these proceeds as a result of certain contingencies such as competitive developments, the results of our commercialization efforts, acquisition and investment opportunities and other factors. Pending use of the proceeds as described above, we intend to invest the net proceeds of this offering in short- and intermediate-term, interest-bearing obligations, investment-grade instruments, certificates of deposit or direct or guaranteed obligations of the U.S. government.

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 invest in our common stock, your interest will be diluted to the extent of the difference between the price per share you pay in this offering and the net tangible book value per share of our common stock immediately after this offering. The net tangible book value of our shares as of September 30, 2020 was \$196.9 million, or \$4.46 per share based upon 44,204,745 shares outstanding as of September 30, 2020. Net tangible book value per share is equal to our total tangible assets, less our total liabilities, divided by the total number of shares outstanding as of September 30, 2020.

After giving effect to the sale of 5,000,000 shares of common stock in this offering after deducting the underwriting discounts and commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of September 30, 2020 would have been \$337.3 million, or \$6.86 per share. This represents an immediate increase in net tangible book value of \$2.40 per share to our existing holders and an immediate decrease in net tangible book value of \$23.14 per share to new investors in this offering.

Dilution per share to new investors is determined by subtracting as-adjusted net tangible book value per share after giving effect to this offering from the public offering price per share paid by new investors. The following table illustrates this dilution on a per share basis.

| | |
|---|----------------|
| Public offering price per share | \$30.00 |
| Net tangible book value per share as of September 30, 2020 | \$4.46 |
| Increase in net tangible book value per share attributable to the offering | <u>2.40</u> |
| As adjusted net tangible book value per share after giving effect to the offering | 6.86 |
| Dilution per share to new investors participating in the offering | <u>\$23.14</u> |

The number of our shares of common stock to be outstanding after this offering is based on 44,204,745 shares outstanding as of September 30, 2020 and excludes:

- 5,096,252 shares of common stock issuable upon the exercise of stock options outstanding as of September 30, 2020, at a weighted average exercise price of \$21.27 per share;
- 2,239,780 shares of common stock reserved for future issuance under our 2017 Plan as of September 30, 2020;
- 1,000,993 shares of common stock reserved for future issuance under the ESPP as of September 30, 2020; and
- 179,662 shares of common stock issuable upon the vesting of restricted stock units outstanding as of September 30, 2020.

The foregoing table does not give effect to the exercise of any outstanding options or the vesting of any restricted stock units outstanding as of September 30, 2020. To the extent options are exercised or restricted stock units vest, there may be further dilution to new investors.

MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES TO NON-U.S. HOLDERS

The following discussion is a summary of the material U.S. federal income tax consequences to Non-U.S. Holders (as defined below) of the purchase, ownership, and disposition of our common stock issued pursuant to this offering, but does not purport to be a complete analysis of all potential tax effects. The effects of other U.S. federal tax laws, such as estate and gift tax laws, and any applicable state, local, or non-U.S. tax laws are not discussed. This discussion is based on the U.S. Internal Revenue Code of 1986, as amended (the “Code”), Treasury Regulations promulgated thereunder, judicial decisions, and published rulings and administrative pronouncements of the U.S. Internal Revenue Service (the “IRS”), in each case in effect as of the date hereof. These authorities may change or be subject to differing interpretations. Any such change or differing interpretation may be applied retroactively in a manner that could adversely affect a Non-U.S. Holder. We have not sought and will not seek any rulings from the IRS regarding the matters discussed below. There can be no assurance the IRS or a court will not take a contrary position to that discussed below regarding the tax consequences of the purchase, ownership, and disposition of our common stock.

This discussion is limited to Non-U.S. Holders that hold our common stock as a “capital asset” within the meaning of Section 1221 of the Code (generally, property held for investment). This discussion does not address all U.S. federal income tax consequences relevant to a Non-U.S. Holder’s particular circumstances, including the impact of the Medicare contribution tax on net investment income and the alternative minimum tax. In addition, it does not address consequences relevant to Non-U.S. Holders subject to special rules, including, without limitation:

- U.S. expatriates and former citizens or long-term residents of the United States;
- persons holding our common stock as part of a hedge, straddle, or other risk reduction strategy or as part of a conversion transaction or other integrated investment;
- banks, insurance companies, and other financial institutions;
- brokers, dealers, or traders in securities;
- “controlled foreign corporations,” “passive foreign investment companies,” and corporations that accumulate earnings to avoid U.S. federal income tax;
- partnerships or other entities or arrangements treated as partnerships for U.S. federal income tax purposes (and investors therein);
- tax-exempt organizations or governmental organizations;
- persons deemed to sell our common stock under the constructive sale provisions of the Code;
- persons who hold or receive our common stock pursuant to the exercise of any employee stock option or otherwise as compensation;
- tax-qualified retirement plans; and
- “qualified foreign pension funds” as defined in Section 897(l)(2) of the Code and entities all of the interests of which are held by qualified foreign pension funds.

If an entity treated as a partnership for U.S. federal income tax purposes holds our common stock, the tax treatment of a partner in the partnership will depend on the status of the partner, the activities of the partnership, and certain determinations made at the partner level. Accordingly, partnerships holding our common stock and the partners in such partnerships should consult their tax advisors regarding the U.S. federal income tax consequences to them.

THIS DISCUSSION IS FOR INFORMATIONAL PURPOSES ONLY AND IS NOT TAX ADVICE. INVESTORS SHOULD CONSULT THEIR TAX ADVISORS WITH RESPECT TO THE APPLICATION OF THE U.S. FEDERAL INCOME TAX LAWS TO THEIR PARTICULAR SITUATIONS AS WELL AS ANY TAX CONSEQUENCES OF THE PURCHASE, OWNERSHIP, AND DISPOSITION OF OUR COMMON STOCK ARISING UNDER THE U.S. FEDERAL ESTATE OR GIFT TAX LAWS OR UNDER THE LAWS OF ANY STATE, LOCAL, OR NON-U.S. TAXING JURISDICTION OR UNDER ANY APPLICABLE INCOME TAX TREATY.

Definition of a Non-U.S. Holder

For purposes of this discussion, a “Non-U.S. Holder” is any beneficial owner of our common stock that is neither a “U.S. person” nor an entity treated as a partnership for U.S. federal income tax purposes. A U.S. person is any person that, for U.S. federal income tax purposes, is or is treated as any of the following:

- an individual who is a citizen or resident of the United States;
- a corporation created or organized under the laws of the United States, 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 that (1) is subject to the primary supervision of a U.S. court and the control of one or more “United States persons” (within the meaning of Section 7701(a)(30) of the Code), or (2) has a valid election in effect to be treated as a United States person for U.S. federal income tax purposes.

Distributions

As described in the section entitled “Dividend Policy,” we do not anticipate declaring or paying dividends to holders of our common stock in the foreseeable future. However, if we do make distributions of cash or property on our common stock, such distributions will constitute dividends for U.S. federal income tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. Amounts not treated as dividends for U.S. federal income tax purposes will constitute a return of capital and first be applied against and reduce a Non-U.S. Holder’s adjusted tax basis in its common stock, but not below zero. Any excess will be treated as capital gain and will be treated as described below under “— Sale or Other Taxable Disposition.”

Subject to the discussion below on effectively connected income, dividends paid to a Non-U.S. Holder will be subject to U.S. federal withholding tax at a rate of 30% of the gross amount of the dividends (or such lower rate specified by an applicable income tax treaty, provided the Non-U.S. Holder furnishes a valid IRS Form W-8BEN or W-8BEN-E (or other applicable documentation) certifying qualification for the lower treaty rate). A Non-U.S. Holder that does not timely furnish the required documentation, but that qualifies 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. Non-U.S. Holders should consult their tax advisors regarding their entitlement to benefits under any applicable income tax treaty.

If dividends paid to a Non-U.S. Holder are effectively connected with the Non-U.S. Holder’s conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, the Non-U.S. Holder maintains a permanent establishment in the United States to which such dividends are attributable), the Non-U.S. Holder will be exempt from the U.S. federal withholding tax described above. To claim the exemption, the Non-U.S. Holder must furnish to the applicable withholding agent a valid IRS Form W-8ECI, certifying that the dividends are effectively connected with the Non-U.S. Holder’s conduct of a trade or business within the United States.

Any such effectively connected dividends will be subject to U.S. federal income tax on a net income basis at the regular rates. A Non-U.S. Holder that is a corporation also may be subject to a branch profits tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty) on such effectively connected dividends, as adjusted for certain items. Non-U.S. Holders should consult their tax advisors regarding any applicable tax treaties that may provide for different rules.

Sale or Other Taxable Disposition

A Non-U.S. Holder will not be subject to U.S. federal income tax on any gain realized upon the sale or other taxable disposition of our common stock unless:

- the gain is effectively connected with the Non-U.S. Holder’s conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, the Non-U.S. Holder maintains a permanent establishment in the United States to which such gain is attributable);
- the Non-U.S. Holder is a nonresident alien individual present in the United States for 183 days or more during the taxable year of the disposition and certain other requirements are met; or
- our common stock constitutes a U.S. real property interest (“USRPI”) by reason of our status as a U.S. real property holding corporation (“USRPHC”) for U.S. federal income tax purposes.

Gain described in the first bullet point above generally will be subject to U.S. federal income tax on a net income basis at the regular rates. A Non-U.S. Holder that is a corporation also may be subject to a branch profits tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty) on such effectively connected gain, as adjusted for certain items.

A Non-U.S. Holder described in the second bullet point above will be subject to U.S. federal income tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty) on gain realized upon the sale or other taxable disposition of our common stock, which may be offset by U.S. source capital losses of the Non-U.S. Holder (even though the individual is not considered a resident of the United States), provided the Non-U.S. Holder has timely filed U.S. federal income tax returns with respect to such losses.

With respect to the third bullet point above, we believe we currently are not, and do not anticipate becoming, a USRPHC. Because the determination of whether we are a USRPHC depends, however, on the fair market value of our USRPIs relative to the fair market value of our non-U.S. real property interests and our other business assets, there can be no assurance we currently are not a USRPHC or will not become one in the future. Even if we are or were to become a USRPHC, gain arising from the sale or other taxable disposition of our common stock by a Non-U.S. Holder will not be subject to U.S. federal income tax if our common stock is “regularly traded,” as defined by applicable Treasury Regulations, on an established securities market and such Non-U.S. Holder owned, actually and constructively, 5% or less of our common stock throughout the shorter of the five-year period ending on the date of the sale or other taxable disposition or the Non-U.S. Holder’s holding period.

Non-U.S. Holders should consult their tax advisors regarding potentially applicable income tax treaties that may provide for different rules.

Information Reporting and Backup Withholding

Payments of dividends on our common stock will not be subject to backup withholding, provided the applicable withholding agent does not have actual knowledge or reason to know the holder is a United States person and the holder either certifies its non-U.S. status, such as by furnishing a valid IRS Form W-8BEN, W-8BEN-E, or W-8ECI, or otherwise establishes an exemption. However, information returns are required to be filed with the IRS in connection with any distributions on our common stock paid to the Non-U.S. Holder, regardless of whether such distributions constitute dividends or whether any tax was actually withheld. In addition, proceeds of the sale or other taxable disposition of our common stock within the United States or conducted through certain U.S.-related brokers generally will not be subject to backup withholding or information reporting if the applicable withholding agent receives the certification described above and does not have actual knowledge or reason to know that such holder is a United States person or the holder otherwise establishes an exemption. Proceeds of a disposition of our common stock conducted through a non-U.S. office of a non-U.S. broker generally will not be subject to backup withholding or information reporting.

Copies of information returns that are filed with the IRS may also be made available under the provisions of an applicable treaty or agreement to the tax authorities of the country in which the Non-U.S. Holder resides or is established.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules may be allowed as a refund or a credit against a Non-U.S. Holder's U.S. federal income tax liability, provided the required information is timely furnished to the IRS.

Additional Withholding Tax on Payments Made to Foreign Accounts

Withholding taxes may be imposed under Sections 1471 to 1474 of the Code (such Sections commonly referred to as the Foreign Account Tax Compliance Act, or "FATCA") on certain types of payments made to non-U.S. financial institutions and certain other non-U.S. entities. Specifically, a 30% withholding tax may be imposed on dividends on, or (subject to the proposed Treasury Regulations discussed below) gross proceeds from the sale or other disposition of, our common stock paid to a "foreign financial institution" or a "non-financial foreign entity" (each as defined in the Code), unless (1) the foreign financial institution undertakes certain diligence and reporting obligations, (2) the non-financial foreign entity either certifies it does not have any "substantial United States owners" (as defined in the Code) or furnishes identifying information regarding each substantial United States owner, or (3) the foreign financial institution or non-financial foreign entity otherwise qualifies for an exemption from these rules. If the payee is a foreign financial institution and is subject to the diligence and reporting requirements in (1) above, it must enter into an agreement with the U.S. Department of the Treasury requiring, among other things, that it undertake to identify accounts held by certain "specified United States persons" or "United States owned foreign entities" (each as defined in the Code), annually report certain information about such accounts, and withhold 30% on certain payments to non-compliant foreign financial institutions and certain other account holders. Foreign financial institutions located in jurisdictions that have an intergovernmental agreement with the United States governing FATCA may be subject to different rules.

Under the applicable Treasury Regulations and administrative guidance, withholding under FATCA generally applies to payments of dividends on our common stock. While withholding under FATCA would have applied also to payments of gross proceeds from the sale or other disposition of stock on or after January 1, 2019, proposed Treasury Regulations eliminate FATCA withholding on payments of gross proceeds entirely. Taxpayers generally may rely on these proposed Treasury Regulations until final Treasury Regulations are issued.

Prospective investors should consult their tax advisors regarding the potential application of withholding under FATCA to their investment in our common stock.

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, BofA Securities, Inc., Cowen and Company, LLC and Stifel, Nicolaus & Company, Incorporated are acting as representatives, have severally agreed to purchase, and we have agreed to sell to them, severally, the number of shares indicated below:

| <u>Name</u> | <u>Number of Shares</u> |
|--|-------------------------|
| Morgan Stanley & Co. LLC | 1,750,000 |
| BofA Securities, Inc. | 1,150,000 |
| Cowen and Company, LLC | 1,125,000 |
| Stifel, Nicolaus & Company, Incorporated | 725,000 |
| Canaccord Genuity LLC | 250,000 |
| Total: | <u>5,000,000</u> |

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 \$1.08 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 750,000 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 750,000 shares of common stock.

| | <u>Per Share</u> | <u>Total</u> | |
|---|------------------|--------------------|----------------------|
| | | <u>No Exercise</u> | <u>Full Exercise</u> |
| Public offering price | \$30.00 | \$150,000,000 | \$172,500,000 |
| Underwriting discounts and commissions to be paid by us | \$ 1.80 | \$ 9,000,000 | \$ 10,350,000 |
| Proceeds, before expenses, to us | \$28.20 | \$141,000,000 | \$162,150,000 |

The estimated offering expenses payable by us, exclusive of the underwriting discounts and commissions, are approximately \$600,000. We have agreed to reimburse the underwriters for expenses relating to clearance of this offering with the Financial Industry Regulatory Authority up to \$25,000.

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

We, our executive officers, our directors and certain shareholders affiliated with our directors have agreed that, without the prior written consent of Morgan Stanley & Co. LLC, BofA Securities, Inc. and Cowen and Company, LLC on behalf of the underwriters, we and they will not, and will not publicly disclose an intention to, during the period ending 90 days in the case of us and our executive officers and 30 days in the case of our directors and their affiliated shareholders after the date of this prospectus supplement (the “restricted period”):

- offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend or otherwise transfer or dispose of, directly or indirectly, any shares of common stock or any securities convertible into or exercisable or exchangeable for shares of common stock;
- file any registration statement with the Securities and Exchange Commission relating to the offering of any shares of common stock or any securities convertible into or exercisable or exchangeable for common stock; or
- enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of the common stock;

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

The restrictions described above do not apply, with respect to our executive officers, directors and shareholders affiliated with our directors, to:

- the transfer of shares as a bona fide gift or gifts;
- transfers or dispositions to any trust for the direct or indirect benefit of such person or the immediate family of such person in transactions not involving a disposition for value;
- transfers or dispositions to any corporation, partnership, limited liability company or other entity all of the beneficial ownership interests of which are held by such person or the immediate family of such person in a transaction not involving a disposition for value;
- transfers or dispositions by will, other testamentary document or intestate succession to the legal representative, heir, beneficiary or a member of the immediate family of such person;
- distributions to partners, members or stockholders of such person;
- the exercise of an option to purchase shares of common stock granted under any equity incentive plan or equity purchase plan described in this prospectus supplement;
- the establishment of a trading plan pursuant to Rule 10b5-1 under the Exchange Act;
- transfers in connection with the termination of employment with the company; and
- transfers or dispositions of shares purchased in this offering or on the open market after the completion of this offering.

The restrictions described above do not apply, with respect to us, to:

- the shares to be sold in this offering;
- the issuance by us of shares of common stock, or securities convertible into, or exercisable for, shares of common stock, pursuant to any employee stock option plan, incentive plan, employee stock purchase plan or stock ownership plan in effect on the date hereof and disclosed in this prospectus supplement;
- the issuance of shares issuable upon the conversion of securities outstanding on the date hereof;

- the filing of one or more registration statements on Form S-8; and
- the offer, issuance and sale of shares of common stock or any securities convertible into, or exercisable, or exchangeable for, shares of common stock in connection with any acquisition or strategic investment (including any joint venture, strategic alliance or partnership) so long as (x) the aggregate number of shares of common stock issued or issuable does not exceed 5% of the number of shares of common stock outstanding immediately after the issuance and sale of the securities and (y) each recipient of any such shares or other securities agrees to lock-up restrictions for the remainder of the restricted period.

Morgan Stanley & Co. LLC, BofA Securities, Inc. and Cowen and Company, LLC, in their sole discretion, may release the common stock and other securities subject to the lock-up agreements described above in whole or in part at any time.

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

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

A prospectus 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 particular, we have entered into a sales agreement with Cowen and Company, LLC, who acts as sales agent under the at-the-market program.

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 “Relevant State”), no securities have been offered or will be offered pursuant to the offering to the public in that Relevant State prior to the

publication of a prospectus in relation to the securities which has been approved by the competent authority in that Relevant State or, where appropriate, approved in another Relevant State and notified to the competent authority in that Relevant State, all in accordance with the Prospectus Regulation, except that offers of securities may be made to the public in that Relevant 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; or
- (c) in any other circumstances falling within Article 1(4) of the Prospectus Regulation,

provided that no such offer of shares shall require us or any underwriter to publish a prospectus pursuant to Article 3 of the Prospectus Regulation or supplement a prospectus pursuant to Article 23 of the Prospectus Regulation.

Each person in a Relevant State who initially acquires any securities or to whom any offer is made will be deemed to have represented, acknowledged and agreed to and with us and the underwriters that it is a qualified investor within the meaning of the Prospectus Regulation.

In the case of any securities being offered to a financial intermediary as that term is used in Article 5(1) of the Prospectus Regulation, each such financial intermediary will be deemed to have represented, acknowledged and agreed that the securities acquired by it in the offer have not been acquired on a non-discretionary basis on behalf of, nor have they been acquired with a view to their offer or resale to, persons in circumstances which may give rise to an offer to the public other than their offer or resale in a Relevant State to qualified investors, in circumstances in which the prior consent of the underwriters has been obtained to each such proposed offer or resale.

We, the underwriters and their affiliates will rely upon the truth and accuracy of the foregoing representations, acknowledgements and agreements.

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

The above selling restriction is in addition to any other selling restrictions set out below.

In connection with the offering, the underwriters are not acting for anyone other than the issuer and will not be responsible to anyone other than the issuer for providing the protections afforded to their clients nor for providing advice in relation to the offering.

United Kingdom

In relation to the United Kingdom (“UK”), no securities have been offered or will be offered pursuant to the offering to the public in the UK prior to the publication of a prospectus in relation to the securities which has been approved by the Financial Conduct Authority in the UK in accordance with the UK Prospectus Regulation and the FSMA, except that offers of securities may be made to the public in the UK at any time under the following exemptions under the UK Prospectus Regulation and the FSMA:

- (a) to any legal entity which is a qualified investor as defined under the UK Prospectus Regulation;
- (b) to fewer than 150 natural or legal persons (other than qualified investors as defined under the UK Prospectus Regulation), subject to obtaining the prior consent of the representatives; or
- (c) at any time in other circumstances falling within section 86 of the FSMA,

provided that no such offer of securities shall require the us or any underwriter to publish a prospectus pursuant to Section 85 of the FSMA or Article 3 of the UK Prospectus Regulation or supplement a prospectus pursuant to Article 23 of the UK Prospectus Regulation.

Each person in the UK who initially acquires any securities or to whom any offer is made will be deemed to have represented, acknowledged and agreed to and with the us and the underwriters that it is a qualified investor within the meaning of the UK Prospectus Regulation.

In the case of any securities being offered to a financial intermediary as that term is used in Article 5(1) of the UK Prospectus Regulation, each such financial intermediary will be deemed to have represented, acknowledged and agreed that the securities acquired by it in the offer have not been acquired on a non-discretionary basis on behalf of, nor have they been acquired with a view to their offer or resale to, persons in circumstances which may give rise to an offer to the public other than their offer or resale in the UK to qualified investors, in circumstances in which the prior consent of the underwriters has been obtained to each such proposed offer or resale.

We, the underwriters and their affiliates will rely upon the truth and accuracy of the foregoing representations, acknowledgements and agreements.

For the purposes of this provision, the expression an “offer to the public” in relation to any securities in the UK means the communication in any form and by any means of sufficient information on the terms of the offer and any securities to be offered so as to enable an investor to decide to purchase or subscribe for any securities, the expression “UK Prospectus Regulation” means Regulation (EU) 2017/1129 as it forms part of domestic law by virtue of the European Union (Withdrawal) Act 2018, and the expression “FSMA” means the Financial Services and Markets Act 2000.

In connection with the offering, the underwriters are not acting for anyone other than the issuer and will not be responsible to anyone other than the issuer for providing the protections afforded to their clients nor for providing advice in relation to the offering.

This document is for distribution only to persons who (i) have professional experience in matters relating to investments and who qualify as investment professionals within the meaning of Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 (as amended, the “Financial Promotion Order”), (ii) are persons falling within Article 49(2)(a) to (d) (“high net worth companies, unincorporated associations etc.”) of the Financial Promotion Order, (iii) are outside the United Kingdom, or (iv) are persons to whom an invitation or inducement to engage in investment activity (within the meaning of Section 21 of the Financial Services and Markets Act 2000, as amended (“FSMA”)) in connection with the issue or sale of any securities may otherwise lawfully be communicated or caused to be communicated (all such persons together being referred to as “relevant persons”). This document is directed only at relevant persons and must not be acted on or relied on by persons who are not relevant persons. Any investment or investment activity to which this document relates is available only to relevant persons and will be engaged in only with relevant persons.

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.

Switzerland

The shares of common stock 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, us, 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 FINMA, 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.

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.

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 shares of our common stock may not be circulated or distributed, nor may the shares of our common stock 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 the SFA, (ii) to a relevant person, 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 shares of our common stock are subscribed or purchased under Section 275 by a relevant person which is: (i) a corporation (which is not an accredited investor) 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 (ii) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary is an accredited investor, shares, debentures and units of shares and debentures of that corporation or the beneficiaries' rights and interest in that trust shall not be transferable for 6 months after that corporation or that trust has acquired shares of our common stock under Section 275 except: (a) to an institutional investor under Section 274 of the SFA or to a relevant person, or any person pursuant to Section 275(1A), and in accordance with the conditions, specified in Section 275 of the SFA; (b) where no consideration is given for the transfer; or (c) by operation of law.

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.

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.

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.

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 Latham & Watkins LLP. The underwriters are being represented by Ropes & Gray LLP in connection with this offering.

EXPERTS

The consolidated financial statements of Rhythm Pharmaceuticals, Inc. appearing in Rhythm Pharmaceuticals, Inc.'s [Annual Report \(Form 10-K\) for the year ended December 31, 2019](#), 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

Available Information

We file reports, proxy statements and other information with the SEC. The SEC maintains a website that contains reports, proxy and information statements and other information about issuers, such as us, who file electronically with the SEC. The address of that website is www.sec.gov.

Our web site address is www.rhythmtx.com. The information on our website, however, is not, and should not be deemed to be, a part of this prospectus supplement.

This prospectus supplement and the accompanying prospectus are part of a registration statement that we filed with the SEC and do not contain all of the information in the registration statement. The full registration statement may be obtained from the SEC or us, as provided below. Documents establishing the terms of the offered securities are or may be filed as exhibits to the registration statement or documents incorporated by reference in the registration statement. Statements in this prospectus supplement or the accompanying prospectus about these documents are summaries and each statement is qualified in all respects by reference to the document to which it refers. You should refer to the actual documents for a more complete description of the relevant matters. You may inspect a copy of the registration statement through the SEC's website, as provided above.

Incorporation by Reference

The SEC's rules allow us to "incorporate by reference" information into this prospectus supplement, which means that we can disclose important information to you by referring you to another document filed separately with the SEC. The information incorporated by reference is deemed to be part of this prospectus supplement, and subsequent information that we file with the SEC will automatically update and supersede that information. Any statement contained in this prospectus supplement or a previously filed document incorporated by reference 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 a subsequently filed document incorporated by reference modifies or replaces that statement.

This prospectus supplement incorporates by reference the documents set forth below that have previously been filed with the SEC:

- [Our Annual Report on Form 10-K for the fiscal year ended December 31, 2019, filed with the SEC on March 2, 2020;](#)
- the information specifically incorporated by reference into our [Annual Report on Form 10-K for the fiscal year ended December 31, 2019](#) from our [definitive proxy statement on Schedule 14A \(other than information furnished rather than filed\)](#), which was filed with the SEC on April 29, 2020;
- Our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2020, June 30, 2020 and September 30, 2020, filed with the SEC on [May 4, 2020](#), [August 3, 2020](#) and [November 2, 2020](#), respectively;
- Our Current Reports on Form 8-K filed with the SEC on [January 8, 2020](#), [February 26, 2020](#), [March 30, 2020](#), [June 18, 2020](#), [July 21, 2020](#), [September 16, 2020](#), [December 11, 2020](#) (as amended on [January 4, 2021](#)), [January 5, 2021](#) and [February 3, 2021](#); and
- [The description of our common stock contained in our registration statement on Form 8-A filed with the SEC on September 29, 2019 and any amendment or report filed with the SEC for the purpose of updating the description.](#)

All reports and other documents we subsequently file pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act prior to the termination of this offering, but excluding any information furnished to, rather than filed with, the SEC, will also be incorporated by reference in this prospectus supplement and deemed to be part of this prospectus supplement from the date of the filing of such reports and documents.

You may request a free copy of any of the documents incorporated by reference in this prospectus supplement by writing or telephoning us at the following:

Rhythm Pharmaceuticals, Inc.
Attention: Secretary
222 Berkeley Street
Boston, MA, 02116
(857) 264-4280

Exhibits to the filings will not be sent, however, unless those exhibits have specifically been incorporated by reference in this prospectus supplement.

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 3 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.

TABLE OF CONTENTS

| | Page |
|--|---------------------------|
| <u>ABOUT THIS PROSPECTUS</u> | <u>ii</u> |
| <u>PROSPECTUS SUMMARY</u> | <u>1</u> |
| <u>RISK FACTORS</u> | <u>3</u> |
| <u>CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING STATEMENTS</u> | <u>3</u> |
| <u>USE OF PROCEEDS</u> | <u>5</u> |
| <u>THE SECURITIES WE MAY OFFER</u> | <u>5</u> |
| <u>DESCRIPTION OF CAPITAL STOCK</u> | <u>6</u> |
| <u>DESCRIPTION OF DEBT SECURITIES</u> | <u>12</u> |
| <u>DESCRIPTION OF WARRANTS</u> | <u>20</u> |
| <u>DESCRIPTION OF UNITS</u> | <u>22</u> |
| <u>SELLING STOCKHOLDERS</u> | <u>22</u> |
| <u>PLAN OF DISTRIBUTION</u> | <u>23</u> |
| <u>LEGAL MATTERS</u> | <u>26</u> |
| <u>EXPERTS</u> | <u>26</u> |
| <u>WHERE YOU CAN FIND MORE INFORMATION</u> | <u>26</u> |
| <u>INCORPORATION OF CERTAIN INFORMATION BY REFERENCE</u> | <u>27</u> |

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 restated 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 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 overallocate in connection with the offering, creating a short position for their own accounts. In addition, to cover overallocations 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.



5,000,000 Shares

RHYTHM PHARMACEUTICALS, INC.

Common Stock

PROSPECTUS SUPPLEMENT

MORGAN STANLEY BofA SECURITIES COWEN

STIFEL

CANACCORD GENUITY

February 4, 2021
