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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

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

For the fiscal year ended December 31, 2020
OR

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

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

RHYTHM PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

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

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

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

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

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

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

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

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐
Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

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

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

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

Large accelerated filer ☒	Accelerated filer ☐
Non-accelerated filer ☐	Smaller reporting company ☐
	Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐
Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☒
Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒.

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant was approximately $828.1 million, based on the closing price of the registrant's Common Stock on June 30, 2020, the last business day of the registrant's most recently completed second fiscal quarter. Solely for purposes of this disclosure, Common Stock held by executive officers, directors and certain stockholders of the registrant as of such date have been excluded because such holders may be deemed to be affiliates.
There were 50,181,164 shares of the registrant's Common Stock outstanding as of February 19, 2021.

DOCUMENTS INCORPORATED BY REFERENCE

The registrant intends to file a definitive proxy statement for the registrant's 2021 Annual Meeting of Stockholders within 120 days of the end of the fiscal year ended December 31, 2020. Portions of such definitive proxy statement are incorporated by reference into Part III of this Annual Report on Form 10-K.

RHYTHM PHARMACEUTICALS, INC.
ANNUAL REPORT ON FORM 10-K
For the Year Ended December 31, 2020

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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K, or this Annual Report, contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, and is subject to the "safe harbor" created by those sections. Any statements about our expectations, beliefs, plans, objectives, assumptions or future events or performance are not historical facts and may be forward-looking. Some of the forward-looking statements can be identified by the use of forward-looking terms such as "anticipates," "believes," "could," "estimates," "expects," "intends," "may," "might," "likely," "plans," "potential," "predicts," "projects," "seeks," "should," "target," "will," "would," or similar expressions and the negatives of those terms include forward-looking statements that involve risks and uncertainties. Forward-looking statements include, but are not limited to, statements regarding proceeds from the Rare Pediatric Disease Priority Review Voucher, or PRV Transfer, the marketing and commercialization of IMCIVREE (setmelanotide), and the timing of commercialization, 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, sources of future financing and sufficiency of cash, our ability to hire and retain necessary personnel, patient enrollments and the timing thereof, the timing of announcements regarding results of clinical trials and filing of regulatory applications, 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 COVID-19 pandemic on our business and operations and our future financial results, and the impact of accounting pronouncements. 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. We cannot guarantee future results, levels of activity, performance or achievements, and you should not place undue reliance on our forward-looking statements. Our actual results may differ significantly from the results discussed in the forward-looking statements. Important factors that might cause such a difference include, but are not limited to, those set forth in Item 1A. "Risk Factors" and elsewhere in this Annual Report. 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 may be required by law, we have no plans to update our forward-looking statements to reflect events or circumstances after the date of this Annual Report. We caution readers not to place undue reliance upon any such forward-looking statements, which speak only as of the date made.

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

TRADEMARKS, TRADENAMES AND SERVICE MARKS

This Annual Report may include trademarks, tradenames and service marks that are the property of other organizations. Solely for convenience, trademarks and tradenames referred to in this Annual Report 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.

SUMMARY RISK FACTORS

Our business is subject to numerous risks and uncertainties, including those described in Part I, Item 1A. "Risk Factors" in this Annual Report. You should carefully consider these risks and uncertainties when investing in our common stock. The principal risks and uncertainties affecting our business include the following:

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

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

- The COVID-19 pandemic has and may continue to adversely impact our business, including our preclinical studies, clinical trials and our commercialization prospects.

- We have only one approved product, which is still in clinical development in additional indications, and we may not be successful in any future efforts to identify and develop additional product candidates.

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

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

- The number of patients suffering from each of the MC4R pathway deficiencies is small and has not been established with precision. If the actual number of patients with any of these conditions is smaller than we had estimated, our revenue and ability to achieve profitability will be materially adversely affected. Moreover, our ability to recruit patients to our trials may be materially adversely affected. Patient enrollment may also be adversely affected by competition and other factors.

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

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

- Even if we complete the necessary clinical trials, the regulatory and marketing approval process is expensive, time consuming and uncertain and may prevent us from obtaining additional approvals for the commercialization of setmelanotide beyond FDA approval for obesity due to proopiomelanocortin, or POMC, proprotein convertase subtilisin/kexin type 1, or PCSK1, or leptin receptor, or LEPR, deficiencies in the United States. We depend entirely on the success of setmelanotide, and we cannot be certain that we will be able to obtain additional regulatory approvals for, or successfully commercialize, setmelanotide. If we are not able to obtain, or if there are delays in obtaining, required additional regulatory approvals, we will not be able to commercialize setmelanotide in additional indications in the United States or in foreign jurisdictions, and our ability to generate revenue will be materially impaired.

- 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.

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

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

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

PART I

Item 1. Business

Overview

We are a commercial-stage biopharmaceutical company focused on changing the paradigm for the treatment of rare genetic diseases of obesity, which are characterized by early-onset, severe obesity and an insatiable hunger or hyperphagia. While obesity affects hundreds of millions of people worldwide, we are advancing a precision medicine strategy for a subset of individuals whose severe obesity is due to genetic variants that impair the melanocortin-4 receptor, or MC4R, pathway, a pathway in the brain that is responsible for regulating hunger, caloric intake and energy expenditure, which consequently affect body weight. Our targeted therapy, IMCIVREE™ (setmelanotide), for which we hold worldwide rights, was approved in November 2020 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, or POMC, proprotein convertase subtilisin/kexin type 1, or PCSK1, or leptin receptor, or LEPR, deficiency confirmed by genetic testing. As we prepare to make IMCIVREE commercially available to patients with these initial, ultra-rare indications, we also are advancing a broad clinical development program for setmelanotide in an effort to expand the approved indication to bring this potential therapy to approximately 100,000 to 200,000 patients in the United States and a similarly-sized rare patient population in Europe.

Upon FDA approval in November 2020, IMCIVREE became the first FDA-approved therapy for use in patients with obesity due to POMC, PCSK1 or LEPR deficiencies. The approval was based on Phase 3 data demonstrating a statistically significant and clinically meaningful impact on weight loss and hunger in patients 12 years old or older with severe obesity due to POMC, PCSK1 or LEPR deficiency. A Marketing Authorization Application, or MAA, seeking approval for setmelanotide for the treatment of obesity and the control of hunger associated with confirmed biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency obesity or confirmed biallelic leptin receptor (LEPR) deficiency obesity in adults and children 6 years of age and above is currently under review by the European Medicines Agency, or EMA, and we expect to obtain regulatory approval from the EMA and make IMCIVREE commercially available in Europe in POMC, PCSK1 and LEPR deficiency obesities in the second half of 2021. Additionally, 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 study met its primary and all key secondary endpoints, demonstrating statistically significant and clinically meaningful reductions in weight and hunger scores, with patients with BBS comprising all primary endpoint responders. No patients with Alström syndrome met the primary endpoint. We are continuing to analyze the full data from patients with BBS or Alström syndrome, which we plan to present at a medical meeting in the first half of 2021. We plan to complete regulatory submissions to both the FDA and the EMA for BBS in the second half of 2021, and we expect to determine next steps for Alström syndrome upon completing a full analysis of the final data from the Phase 3 trial.

We also are advancing a broad clinical development program evaluating setmelanotide in several ongoing and planned clinical trials, and leveraging the largest known DNA database focused on obesity - with approximately 37,500 sequencing samples as of September 30, 2020 - to improve the understanding, diagnosis and care of people living with severe obesity due to certain variants in genes associated with the MC4R pathway. In January 2021, we announced positive

proof-of-concept data from our ongoing exploratory Phase 2 Basket Study evaluating setmelanotide in patients with MC4R pathway deficiencies due to a variant in one of the two alleles in the *POMC, PCSK1*, or *LEPR* genes, as well as the *SRC1* and *SH2B1* genes. Based on those interim data and results from our sequencing database, we announced plans to initiate a potentially registration-enabling Phase 3 trial in the second half of 2021 evaluating setmelanotide in patients with obesity due to a variant in one of the two alleles in the *POMC, PCSK1,* or *LEPR* genes, or HET obesity, as well as the *SRC1* and *SH2B1* genes, pending further discussions with the FDA and MAA. We anticipate announcing top-line data from an additional genetically defined cohort, MC4R-rescuable, from this same study in the first half of 2021. In addition, we announced plans for an expanded Phase 2 Basket Study to evaluate setmelanotide for the treatment of obesity due to a deficiency in one of 31 additional genes associated with the MC4R pathway in the second half of 2021. Our broad clinical program evaluating setmelanotide in rare diseases of obesity also includes plans to initiate a Phase 2 study evaluating setmelanotide in patients with hypothalamic obesity in the first half of 2021, a Phase 2 study in pediatric patients with MC4R pathway deficiencies between the ages of 2 and 6 years old in the second half of 2021, and a potential registration-enabling study with our once-weekly formulation of setmelanotide in the second half of 2021.

While obesity is a complex problem with a variety of contributing and causal factors such as genetics and a wide range of environmental influences, we are taking a simple, three-step approach in our clinical development programs that we expect will translate to the real-world practice of medicine. First, we will identify patients with early-onset severe obesity (BMI>40 kg/m^2 in adults or BMI≥ 95th percentile for age and gender for patients 6 to 16 years of age) and hyperphagia. Second, with genetic testing, we will seek to confirm that these patients have a defect in one of 36 genes (or more) related to the MC4R pathway. If these individuals test positive for such a genetic defect, they would be eligible for enrollment in a clinical trial evaluating setmelanotide. In clinical trials across several different genetic deficiencies, we have seen patients respond with rapid weight loss of 5 percent or more in 12 to 16 weeks. Based on our experience treating up to more than 100 patients in our Phase 2 and Phase 3 clinical studies, patients who achieve 5 percent weight loss at approximately 12 to 16 weeks on setmelanotide therapy tend to achieve 10 percent weight loss within a year, hence we deem these patients to be responders. Weight loss of this magnitude, particularly in patients with severe, early-onset obesity, is considered clinically-meaningful.

Our sequencing-based epidemiology estimates show that each of these genetically-defined MC4R pathway deficiencies number in the rare or ultra-rare category, according to established definitions of rare disease patient populations. Our epidemiology estimates are approximately 5,000 for U.S. patients in initial indications, including obesity due to homozygous POMC, PCSK1 or LEPR deficiencies, and BBS and Alström syndrome. The epidemiology estimates for the indications studied in our ongoing exploratory Phase 2 Basket Study (HETs and SRC1 or SH2B1 deficiency) suggest that between 100,000 to 200,000 U.S. patients with one of these genetic deficiencies have the potential to respond to setmelanotide. Despite the potential addressable patient population likely being larger than ultra-rare populations, these patients face similar challenges as other patients with rare diseases, namely lack of awareness, resources, tests, tools and especially therapeutic options.

We are pushing to expand the potential global market for IMCIVREE beginning with obesities from POMC, PCSK1 and LEPR deficiencies and lay the groundwork for regulatory submissions in BBS and potentially Alström syndrome. As we significantly expand our clinical development programs, our disease awareness and patient finding efforts are aligned with a singular focus on building a community of caregivers and healthcare providers focused on transforming the treatment of these diseases. We have medical science liaisons and disease education liaisons in the field in the United States and Europe engaging with physicians who treat patients with severe obesity. We continue to bring health care providers together with our Genetic Obesity Learning Development (GOLD) Academy, a series of U.S. based non-CME programs we sponsor. And our sequencing efforts, now primarily focused on our Uncovering Rare Obesity™ sponsored genetic testing program, fuel MC4R pathway research, disease education and awareness and patient finding.

With approximately 90 employees in the United States and Europe, a rapidly expanding network of key opinion leaders, and an increasing number of treated patients, we are focused on the changing the paradigm for the treatment of rare genetic diseases of obesity. Key elements of our strategy include:

- **Systematic approach to understand the genes that are part of the MC4R pathway:** With the largest known obesity DNA database and our approach to translational research and clinical development, we

believe we are uniquely positioned to drive the scientific understanding of the many genes that comprise or affect the function of the MC4R pathway.

- **Rapidly advance development of setmelanotide to address as many patients as possible:** We are focused on expanding commercial availability in the United State, Europe and select other markets, and executing on the clinical trials which will further inform which genes affect the MC4R pathway and, if successful, potentially enable registration of setmelanotide in an expanding number of indications. With multiple planned and ongoing Phase 2 and 3 trials, we anticipate bringing online approximately 50 to 100 clinical trials sites in the United States and Europe. Each of these trial sites will serve as a local hub for as many as five to 10 more hospitals and obesity clinics in our growing referral network, and we will focus marketing and communications efforts geographically to support genetic testing around trial sites in order to build these local referral networks.

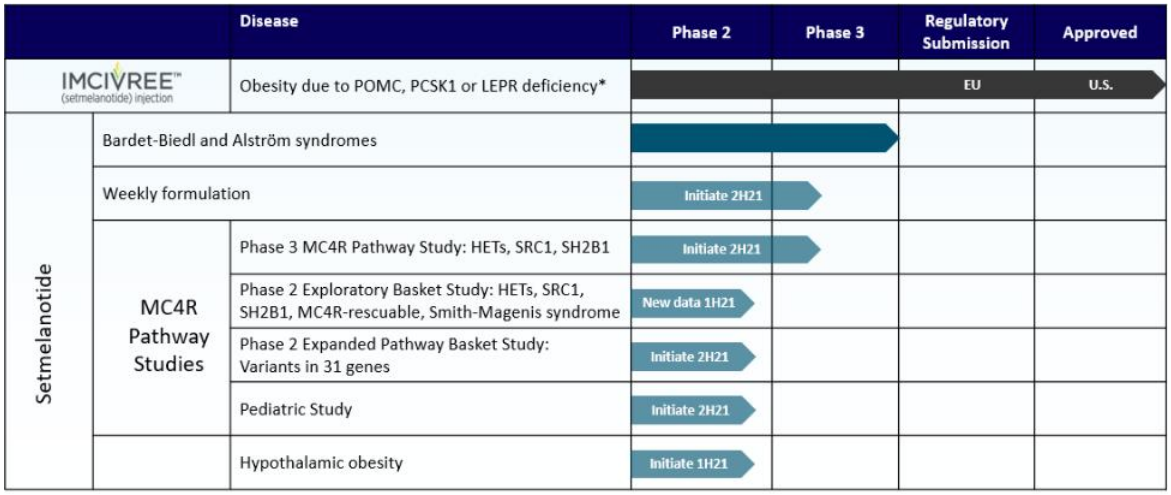
- **Leverage genetic testing programs to feed clinical trial enrollment and commercial launch activities:** We are committed to expanding our obesity DNA database and expanding access and availability to genetic testing for individuals with early-onset, severe obesity and hyperphagia. Approximately 10 to 15 percent of patients with early-onset severe obesity test positive for a defect in one of five MC4R pathway genes proposed to be studied in our upcoming Phase 3 MC4R Pathway Study. We will continue to expand our genetic testing effort focusing initially on clinical trial enrollment and early commercialization efforts. We expect to sequence approximately 10,000 to 20,000 additional obese individuals over the next one to two years with the goal to rapidly increase testing beyond those numbers in subsequent years.

- **Lifecyle Management:** As we make IMCIVREE available in our initial indications and build out our clinical development programs, we are also focused on developing and bringing follow-on product candidates to market, including a weekly formulation of setmelanotide designed to be more convenient and patient-friendly, as well as an auto-injector for the once-weekly formulation. Additionally, we are planning a clinical trial in pediatric patients from 2 years to 5 years in age with obesity due to POMC, PCSK1 or LEPR deficiency and patients with BBS, as we know early-onset obesity manifests between the ages of 2 and 6 years old. We also are exploring more selective and potent MC4R agonists through preclinical development of our library of MC4R agonist candidates.

- **Ensure global access to IMCIVREE:** We are actively pursuing a global strategy for our clinical development, commercial and community building programs. We are building an emerging international organization focused on major markets in Europe, and we are actively exploring distributor opportunities to provide setmelanotide to patients in the Middle East and South America.

Our Product Pipeline

The following chart depicts key information regarding the development of setmelanotide, including the indications we are pursuing within MC4R pathway deficiencies and the current state of development:



** Indicated for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to POMC, PCSK1 or LEPR deficiency confirmed by genetic testing demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance.*

Market Overview

Early-onset, Severe Obesity and the MC4R Pathway

All obesity is not the same, and rare genetic diseases of obesity are distinct from general obesity. The hallmark characteristics of rare genetic diseases of obesity are early-onset, severe obesity and hyperphagia, an overwhelming, heightened, and relentless hunger that drives a severe preoccupation with food and potentially extreme food-seeking behaviors. Diet and lifestyle modifications fail to achieve meaningful weight loss in patients with rare genetic diseases of obesity.

Accordingly, the discovery that the MC4R pathway can regulate both hunger and energy expenditure separately—helping maintain the balance between food intake and energy burn—has defined an important target for therapeutics. In addition to obesity due to POMC, PCSK1 or LEPR deficiencies, recent advances in genetic studies have identified several diseases characterized at least in part with early-onset, severe obesity and hyperphagia that are the result of genetic defects affecting the MC4R pathway, including BBS, Alström syndrome, POMC, PCSK1, and LEPR HETs, SRC1 deficiency obesity, SH2B1 deficiency obesity, MC4R deficiency obesity and deficiencies in upwards of 31 additional MC4R-related genes. With a deeper understanding of this critical signaling pathway, we are taking a different approach to drug development by focusing on specific genetic deficiencies affecting the MC4R pathway. We believe that this approach has the potential to provide dramatic improvements in weight and appetite by restoring lost function in the MC4R pathway.

Obesity Caused by Rare Genetic Deficiencies Affecting the MC4R Pathway

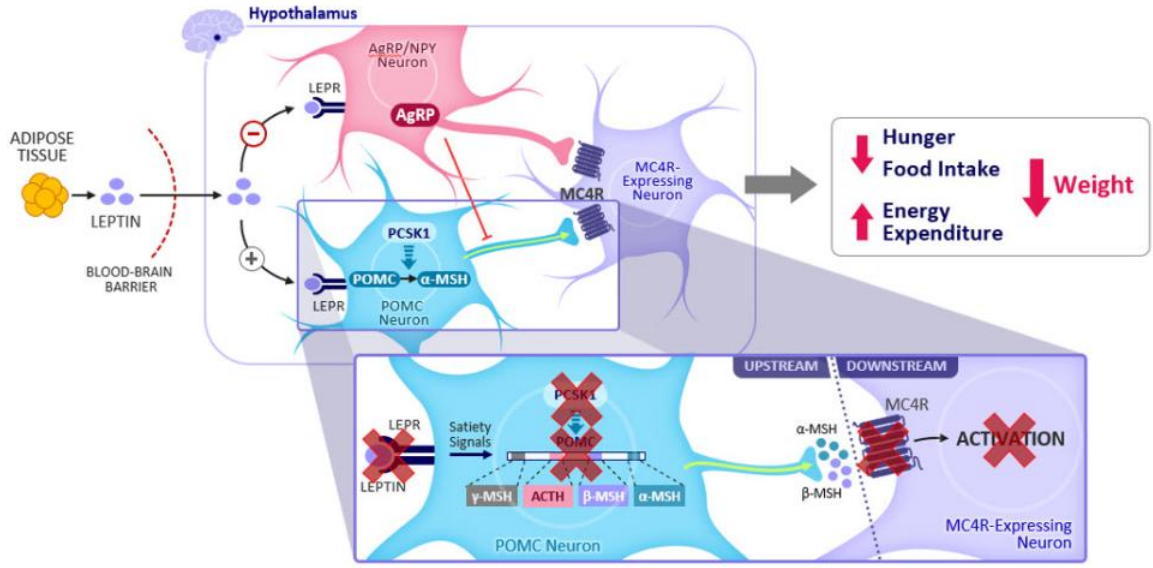
The MC4R pathway, which has been the focus of extensive scientific investigation for many years, regulates hunger, caloric intake, and energy expenditure, which consequently affect body weight. The critical role of the MC4R

pathway in weight regulation is supported by the observation that single gene defects at many points in this pathway result in early-onset, severe obesity.

The MC4R pathway is illustrated in the figure below. Under normal conditions, POMC neurons are activated by brain satiety signals, including those resulting from the hormone leptin acting through LEPR. POMC neurons produce a protein, which is processed by the PCSK1 enzyme, into melanocyte stimulating hormone, or MSH, the natural ligand, or activator of the MC4R. When upstream genetic mutations disrupt this pathway, it can lead to insufficient MC4R activation and the result is hyperphagia, or insatiable hunger, and severe obesity.

The figure below also illustrates some of the genes that are upstream of the MC4R and the potential effect deficiencies in those genes may have on the activation of the MC4R, which regulates hunger and energy expenditure.

Setmelanotide Development Targets: Upstream Deficiencies Affecting the MC4R Pathway



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

We are focused on developing setmelanotide for genetic disorders that arise due to defects in this pathway that are upstream of MC4R. With our expanding clinical development program, we plan to evaluate setmelanotide in Phase 2 and 3 trials for the treatment of obesity due to a deficiency in one of 36 genes associated with the MC4R pathway. Setmelanotide has the potential to restore lost function in this pathway by activating the intact MC4R pathway below the genetic defect. In this way, we believe setmelanotide acts as restorative therapy.

Epidemiology Estimates of Rare Genetic Diseases of the MC4R Pathway

While obesity is epidemic in the United States and elsewhere, we are focused on rare genetic diseases of obesity, most often characterized by early-onset, severe obesity and unrelenting hunger or hyperphagia. Of the tens of millions of obese individuals in the United States, we estimate that there are approximately 5 million individuals whose severe obesity was early-onset, as the table below summarizes the indications currently approved or under active clinical investigation.

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

Obesity due to POMC or PCSK1 deficiency	~100 – 500 U.S. patients
Obesity due to LEPR deficiency	~500 – 2,000 U.S. patients
Bardet-Biedl syndrome	~1,500 - 2,500 U.S. patients
Alström syndrome	~500 U.S. patients
POMC, PCSK1, or LEPR heterozygous deficiency obesities; SRC1 and SH2B1 deficiency obesities.	~100,000 – 200,000 U.S. patients
MC4R deficiency obesity	~10,000* U.S. patients
Smith-Magenis syndrome	~ 2,400** U.S. patients

These calculations rely on internal and proprietary sequencing data and assume a U.S. population of 327 million, of which 1.7% have early-onset, severe obesity (Hales et al in JAMA – April 2018: Trends in Obesity and Severe Obesity Prevalence in US Youth and Adults by Sex and Age, 2007-2008 to 2015-2016); * Estimated prevalence of U.S. patients with rescuable variants of the MC4R; ** Published prevalence estimates of one in 25,000 in the United States, and 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.

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

For patients with genetic forms of MC4R pathway deficiencies, the rarity and the genetic pathophysiology of our target indications means that there is no comprehensive patient registry or other method of establishing with precision the actual number of patients. As a result, we have had to rely on other available sources to derive clinical prevalence estimates for our target indications. We recently updated our prevalence estimates in January 2021 based on sequencing data from approximately 37,500 obese individuals and rates of response to setmelanotide in our exploratory Phase 2 Basket study. Because 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 under- or overestimate the addressable population. While our projected estimates of the aggregate total addressable population continues to expand with the addition of new genes, the addressable population faces the challenges of a rare disease population. The disease must be suspected by the physician, confirmed by genetic testing and then setmelanotide responsiveness confirmed by a 12-16 week trial with the product candidate.

Limitations of Current Therapies

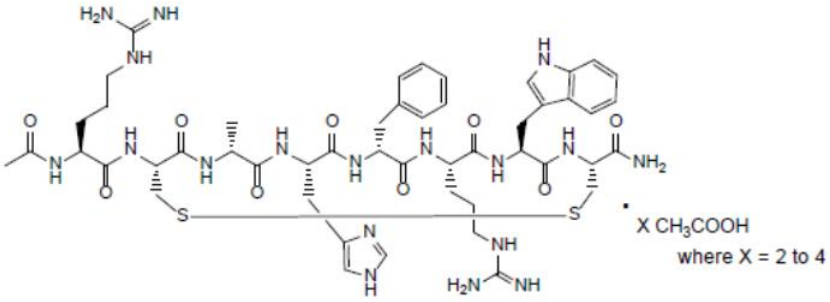
Although drugs approved for general obesity can potentially be used in obese patients with MC4R pathway deficiencies, all have limited efficacy and aim to treat symptoms rather than addressing the underlying biology. Many weight loss drugs interfere with normal physiologic function to induce weight loss. For example, drugs which delay gastric emptying may cause a patient to feel full and eat less, but are also often associated with nausea and vomiting as a consequence of the delayed emptying. In the case of individuals with MC4R pathway deficiencies, these therapies also do not specifically address the hunger which accompanies the MC4R deficiency. Similarly, bariatric surgery which has been shown to be quite effective in the general obese population, may be unsuccessful in the MC4R pathway deficient patient for the same reason. The stomach is smaller but the hunger drive persists and weight gain continues.

IMCIVREE™ (setmelanotide): First-ever Therapy for Chronic Weight Management in Adult and Pediatric Patients Six Years of Age and Older with Obesity Due to POMC, PCSK1 or LEPR Deficiency Confirmed by Genetic Testing

On November 27, 2020, we announced that the FDA approved IMCIVREE for chronic weight management in adult and pediatric patients six years of age and older with obesity due to POMC, PCSK1 or LEPR deficiency confirmed by genetic testing. With this approval, IMCIVREE became the first-ever FDA approved therapy for use in patients with these rare genetic diseases of obesity. As an MC4 receptor agonist, IMCIVREE is designed to restore impaired MC4 receptor pathway activity arising due to genetic deficits upstream of the MC4 receptor. We expect to make IMCIVREE commercially available to patients six years of age and older with obesity due to POMC, PCSK1 or LEPR deficiency in the U.S. in the first quarter of 2021.

IMCIVREE contains setmelanotide acetate, a melanocortin 4 (MC4) receptor agonist. Setmelanotide is an 8 amino acid cyclic peptide analog of endogenous melanocortin peptide α-MSH. The chemical name for setmelanotide acetate is acetyl-L-arginyl-L-cysteinyl-D-alanyl-L-histidinyl-D-phenylalanyl-L-arginyl-L-tryptophanyl-L-cysteinamide cyclic (2→8)-disulfide acetate. Its molecular formula is C49H68N18O9S2 (anhydrous, free-base), and molecular mass is 1117.3 Daltons (anhydrous, free-base).

The chemical structure of setmelanotide is:



IMCIVREE injection is a sterile, clear to slightly opalescent, colorless to slightly yellow solution. Each 1 mL of IMCIVREE contains 10 mg of setmelanotide provided as setmelanotide acetate, which is a salt with 2 to 4 molar equivalents of acetate, and the following inactive ingredients: 100 mg N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl- glycero-3- phosphoethanolamine sodium salt, 8 mg carboxymethylcellulose sodium (average MWt 90,500), 11 mg mannitol, 5 mg phenol, 10 mg benzyl alcohol, 1 mg edetate disodium dihydrate, and Water for Injection. The pH of IMCIVREE is 5 to 6.

Obesity due to POMC, PCSK1 or LEPR deficiency are ultra-rare diseases caused by variants in *POMC, PCSK1* or *LEPR* genes that impair the MC4 receptor pathway. People living with obesity due to POMC, PCSK1 or LEPR deficiency struggle with extreme, insatiable hunger beginning at a young age, resulting in early-onset, severe obesity.

Obesity due to POMC or PCSK1 deficiency is caused by the loss of both genetic copies of either the gene for POMC or the gene for PCSK1. This results either in loss of POMC neuropeptide synthesis, in the case of biallelic (compound heterozygous and homozygous) deficiency in the POMC gene, or in disruption of the required processing of the POMC neuropeptide product to MSH by the PCSK1 enzyme, in the case of biallelic deficiency in the PCSK1 gene. The result of both of these two biallelic genetic defects is lack of MSH to bind and activate MC4R, ultimately leading to the lack of stimulation of downstream MC4R neurons and causing severe, early-onset obesity and hyperphagia. POMC or

PSCK1 biallelic deficiency may also be associated with hormonal deficiencies, such as hypoadrenalism, as well as red hair and fair skin.

POMC/PCSK1 deficiency is characterized by voracious infant feeding, rapid weight gain and severe obesity, often in early infancy, with patients demonstrating remarkable weight increases many standard deviations from the normal weight growth curves. These patients and their caregivers have attempted to stabilize body weight with the help of psychologists, nutritionists and pediatric endocrinologists, all without significant success.

Obesity due to LEPR deficiency is an ultra-rare genetic disease that causes hyperphagia and severe, early-onset obesity. Leptin's role in obesity has been elucidated by characterization of severely obese people with biallelic mutations that impair the activity of leptin, including disruption of signaling at the LEPR, known as LEPR deficiency obesity. Under normal conditions, leptin can activate POMC neurons and the downstream MC4R, but like other deficiencies upstream in the MC4R pathway, lack of signaling at LEPR results in loss of function in the MC4R pathway.

Pivotal Phase 3 Clinical Trials Evaluating Setmelanotide in POMC and LEPR Deficiency Obesities

We assessed the safety and efficacy of IMCIVREE in two pivotal trials that were identically designed: one-year, open-label studies, each with an eight-week, double-blind withdrawal period. The studies enrolled patients with homozygous or presumed compound heterozygous pathogenic, likely pathogenic variants, or VUS, for either the POMC, PCSK1 or LEPR gene. In both studies, adult patients had a body mass index (BMI) of ≥30 kg/m2. Weight in pediatric patients was ≥95th percentile using growth chart assessments.

Efficacy analyses were conducted in 21 patients who had completed at least one year of treatment at the time of a pre-specified data cutoff. Of the 21 patients included in the efficacy analysis in both pivotal studies, 62 percent were adults and 38 percent were aged 16 years or younger. In Study 1, 50 percent of patients were female, 70 percent were White, and the median BMI was 40.0 kg/m^2 (range: 26.6-53.3) at baseline. In Study 2, 73 percent of patients were female, 91 percent were White, and the median BMI was 46.6 kg/m^2 (range: 35.8-64.6) at baseline.

In the POMC/PCSK1 study, 80 percent of patients with obesity due to POMC or PCSK1 deficiency met the primary endpoint, achieving a ≥10 percent weight loss after one year of treatment with IMCIVREE. In the LEPR study, 46 percent of patients with obesity due to LEPR deficiency achieved a ≥10 percent weight loss after 1 year of treatment with IMCIVREE.

Proportion of Patients Achieving at Least 10 percent Weight Loss from Baseline at 1 Year in Study 1 and Study 2

Parameter	**Statistic**	**Study 1 (POMC) (N=10)**	**Study 2 (LEPR) (N=11)**
Patients Achieving at Least 10% Weight Loss at Year 1	n (%)	8 (80.0%)	5 (45.5%)
	95% CI[1]	(44.4%, 97.5%)	(16.8%, 76.6%)
	P-value[2]	<0.0001	0.0002

Note: The analysis set includes patients who received at least 1 dose of study drug and had at least 1 baseline assessment.
1 From the Clopper-Pearson (exact) method
2 Testing the null hypothesis: Proportion =5%

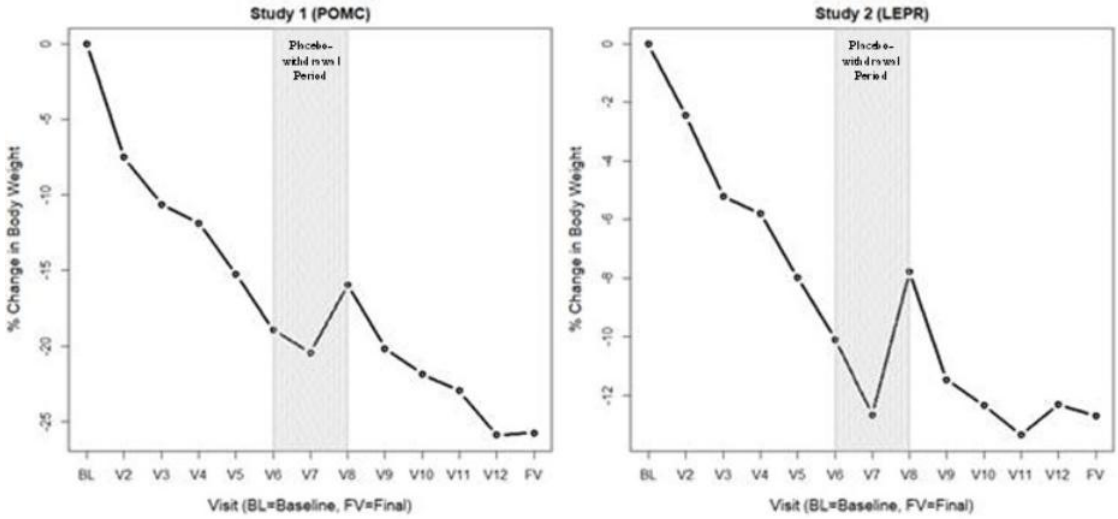
Percent Change from Baseline in Weight at 1 Year in Studies 1 and 2 (Full Analysis Set)

Parameter	**Statistic**	**Study 1 (POMC) (N=10)**	**Study 2 (LEPR) (N=11)**
Baseline Body Weight (kg)	Mean (SD)	118.7 (37.5)	133.3 (26.0)
	Median	115.0	132.3
	Min, Max	55.9, 186.7	89.4, 170.4

Parameter	Statistic	Study 1 (POMC) (N=10)	Study 2 (LEPR) (N=11)
1-Year Body Weight (kg)	Mean (SD)	89.8 (29.4)	119.2 (27.0)
	Median	84.1	120.3
	Min, Max	54.5, 150.5	81.7, 149.9
Percent Change from Baseline to 1 Year (%)	Mean (SD)	-23.1 (12.1)	-9.7 (8.8)
	Median	-26.7	-9.8
	Min, Max	-35.6, -1.2	-23.3, 0.1
	LS Mean[1]	-23.12	-9.65
	95% CI[1]	(-31.9, -14.4)	(-16.0, -3.3)
	P-value[2]	0.0003	0.0074
Note: This analysis includes patients who received at least 1 dose of study drug, had at least 1 baseline assessment. 1 ANCOVA model containing baseline body weight as a covariate 2 Testing the null hypothesis: mean percent change=0			

When treatment with IMCIVREE was withdrawn in the 16 patients who had lost at least 5 kg (or 5 percent of body weight if baseline body weight was <100 kg) during the 10-week open-label period, these patients gained an average of 5.5 kg in Study 1 and 5.0 kg in Study 2 over 4 weeks. Re-initiation of treatment with IMCIVREE resulted in subsequent weight loss.

Mean Percent Change in Body Weight from Baseline by Visit (Study 1 [N=9] and Study 2 [N=7])



BL=Baseline (day of first dose)
V2 to V3 = variable dose titration period (2 to 12 weeks)
V3 to V6 = 10-week open-label treatment period
V6 to V8 = 8-week placebo withdrawal period (4 weeks active, 4 weeks placebo)
V8 to V12 = 32-week open-label treatment period
FV = Final visit; time point for primary efficacy analysis
Note: This figure includes patients who had lost at least 5 kg (or 5% of body weight if baseline body weight was <100 kg) during the 10-week open-label period.

Additionally, as of April 16, 2020, a total of 15 patients who participated in the pivotal studies were being treated in our long-term extension study, including nine with POMC deficiency obesity and six with LEPR deficiency obesity, all of whom previously completed one of our two pivotal Phase 3 trials evaluating setmelanotide for the treatment of severe obesity and insatiable hunger. As of that date, extension study data showed durable weight loss with long-term treatment with setmelanotide for a total of up to 155 weeks. Hunger scores have typically remained stable throughout the extension study. Treatment in the extension study remains ongoing, and as of November 16, 2020, 12 of 15 eligible POMC patients and 12 of 15 eligible LEPR patients had been enrolled in the long-term extension study.

Also as of April 16, 2020, we had enrolled a total of eight patients, including four pediatric patients between the ages 6 and 12 years old, in supplemental cohorts in these Phase 3 trials for POMC deficiency obesity and LEPR deficiency obesity, with four supplemental patients enrolled in each trial. All eight supplemental patients achieved the primary endpoint of 10 percent or greater weight loss at 52 weeks on setmelanotide therapy, as calculated under the same statistical analysis plan used in the pivotal trials. All of the supplemental patients were enrolled by European investigators, as were most of the patients in the pivotal cohorts. The mean reduction in baseline body weight for the supplemental POMC deficiency obesity patients was -26.3 percent, and the mean reduction in body weight for the supplemental LEPR deficiency obesity patients was -13.2 percent. The estimated mean percentage reduction in most hunger score for evaluable patients in the supplemental cohorts was -57.3 percent. Hunger scores collected from children younger than 12 were calculated differently and therefore not counted in this analysis. Combining data from the eight supplemental patients with data from the pivotal cohorts, 12 out of 14 patients with POMC deficiency obesity and 9 out of 15 patients with LEPR deficiency obesity achieved the primary endpoints of greater than 10 percent weight loss over approximately one year. Additionally, the data for all key secondary endpoints from the supplemental cohorts were consistent with the data from the pivotal cohorts.

EU Regulatory Path

Our MAA seeking approval for setmelanotide the treatment of obesity and the control of hunger associated with confirmed biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency obesity or confirmed biallelic leptin receptor (LEPR) deficiency obesity in adults and children 6 years of age and above is currently under review by the EMA, having been submitted in June 2020. The EMA has previously granted PRIority MEdicines (PRIME) designation for setmelanotide for the treatment of obesity and the control of hunger associated with deficiency diseases of the MC4 receptor pathway.

Commercial Availability

We are focused on making IMCIVREE available globally as we build an infrastructure to bring this precision therapy to patients with obesity due to POMC, PCSK1 or LEPR deficiency. We aim to ensure a positive experience for patients, caregivers and prescribing physicians, and delivering on that promise with an efficient scalable model. We expect IMCIVREE to be commercially available in the United States in the first quarter of 2021. We will achieve this through efforts in partnership with our specialty pharmacy, which will serve as the primary point of contact for patients and health care providers, or HCPs. We are committed to providing comprehensive patient support offerings and will provide additional details on our patient support program when IMCIVREE becomes commercially available. We believe these activities will also lay the groundwork for future potential launches while ensuring ongoing seamless support to patients within our current approval.

We are working with the broader community of physicians, patients and families to improve the path to an accurate diagnosis. Patient identification is a core focus of our cross-functional teams. We support disease education through our medical and commercial team efforts. Our medical field team consists of 10 medical science liaisons and eight disease education liaisons who have reached out to hundreds of HCPs to educate them on the MC4R pathway and the underlying genetics that may lead to obesity. We have supplemented these one-on-one interactions with engagement of HCPs through our GOLD Academy program. The commercial team also supports disease education with non-personal promotion activities to reach a larger group of HCPs and patients, who may access additional educational information on our website addressing rare genetic diseases of obesity awareness (www.leadforrareobesity.com). Once an HCP suspects a patient may have a genetic cause for their obesity, we will make available our free Uncovering Rare Obesity (URO) testing program, which screens a panel of genes involved in the MC4R pathway. The URO testing program supports the identification of patients eligible within the indications on the IMCIVREE label, as well as other genes of interest to us, including BBS, Alström, and genes expected to be included in our expanded Phase 2 Basket Study.

In addition to having disease education and testing initiatives, we have patient support programs in place to provide support to patients, including genetic counseling, reimbursement support inclusive of co-pay and patient assistance programs, and IMCIVREE injection training.

Although the total number of patients potentially addressable by setmelanotide may not be so rare, individually populations with each of these MC4R pathway-related genetic defects are rare and affected patients face many of the same challenges as any classically rare patient population. There is little or no awareness about these rare genetic diseases obesity, and the patients suffering from them are lost in the health care system, with limited educational resources and no effective treatments for their condition. All of our efforts and services described above are designed to address the challenges of rare diseases and lay the groundwork for potential future launches, with a focus on scalability .

Development of Setmelanotide for Additional Indications

BBS and Alström Syndrome

Bardet-Biedl Syndrome

Bardet-Biedl syndrome is a life-threatening, ultra-rare orphan disease. BBS is a monogenic disorder that causes severe obesity and hyperphagia as well as vision loss, polydactyly, kidney abnormalities, and other signs and symptoms. For BBS patients, hyperphagia and obesity can have significant health consequences. BBS is part of a class of disorders

called ciliopathies, or disorders associated with the impairment of cilia function in cells. Cilia are hair-like cellular projections that play a fundamental role in the regulation of several biological processes, including satiety signaling. Cilia dysfunction in the hypothalamus is thought to contribute to hyperphagia and obesity in BBS. BBS is a genetically heterogeneous disease that is caused by as many as 21 separate Bardet-Biedl loci defects that result in a similar syndrome. Recent scientific studies identify deficiencies affecting the MC4R pathway as a potential cause of the obesity and hyperphagia associated with BBS and demonstrate that an MC4R agonist can directly impact these symptoms. Currently there are no approved or effective therapies for BBS.

In December 2020, we reported positive topline results from our pivotal Phase 3 clinical trial evaluating setmelanotide for the treatment of insatiable hunger and severe obesity in individuals with BBS or Alström syndrome. The combined pivotal, Phase 3 trial is a multinational, open-label, single-arm study consisting of 52 weeks of treatment with setmelanotide. Participants were blinded and randomized for the first 14 weeks of the trial to receive either placebo or setmelanotide therapy. Those participants who began the trial on setmelanotide continued therapy for a total of 52 weeks, while those on placebo went on to receive 52 weeks of setmelanotide therapy after completion of the 14-week placebo period. All patients were obese, defined as BMI $\geq$30 kg/m^2 for patients $\geq$16 years of age or weight >97th percentile for age and sex on growth chart assessment for patients 6 to 15 years of age. Based on the statistical analysis plan, the primary analysis was completed for 28 of the 31 patients who reached or exceeded 52 weeks on setmelanotide therapy, as well as three patients who were randomized to the placebo group during the 14-week double-blind period, who had not yet reached 52 weeks on therapy. The study met its primary and all key secondary endpoints, demonstrating statistically significant and clinically meaningful reductions in weight and hunger scores, with patients with BBS comprising all primary endpoint responders. No patients with Alström syndrome met the primary endpoint. The analysis of the primary endpoint showed that 11 of 31 (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), 11 of 28 patients with BBS achieved 10 percent reduction in body weight, and 0 of 3 patients with Alström syndrome achieved 10 percent reduction in body weight. The analysis of the key secondary endpoints showed that 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).

We believe the inclusion of adolescents in the primary analysis confounded the weight analysis as they represented approximately half of the patients and were still growing. Of the 28 BBS patients included in the primary analysis set, 15 of them were adults, age 18 or older, and 13 were adolescents. Looking at adults only, 11 out of 15 or 73 percent had greater than 5 percent weight loss. And 8 out of 15 or 53 percent had greater than 10 percent weight loss.

We believe this distinction between adults and adolescents is important because children and adolescents are growing in height and increasing bone mass and therefore would be expected to gain weight. On January 26, 2021, we shared data from a predefined exploratory endpoint showing the impact 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. Setmelanotide was associated with statistically significant and clinically meaningful reductions in BMI-Z scores in patients with BBS. In 16 patients younger than 18 with BBS, 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).

Consistent with prior clinical experience, setmelanotide was generally well tolerated, there were no serious adverse events, or SAEs, related to treatment with setmelanotide and the safety results were consistent with previous setmelanotide clinical trials. Eight patients discontinued from study drug treatment during the trial, five due to adverse events, or AEs (one on placebo at the time), and three for other reasons (one on placebo at the time).

We are continuing to follow patients with BBS who are severely obese and enrolled in our Phase 2 trial. Results from this Phase 2 trial demonstrate that treatment with setmelanotide led to marked reductions in body weight and decreased appetite as shown by lower hunger scores. The results of this study were published in an article entitled, “Effect of Setmelanotide, an MC4R Agonist, on Obesity in Bardet-Biedl Syndrome,” in July 2020 in the peer-reviewed journal *Diabetes, Obesity and Metabolism*. Previously, we reported in September 2019 that six of the nine patients showed clinically important, marked weight loss. In the second quarter of 2018, the FDA agreed to include BBS under our existing Breakthrough Therapy designation for setmelanotide.

We anticipate completion of regulatory submissions to both the FDA and the EMA seeking marketing authorization for setmelanotide for the treatment of obesity in patient with BBS in the second half of 2021.

Alström Syndrome

Alström syndrome is a life-threatening, ultra-rare orphan disease. It is a monogenic disorder that causes childhood obesity and hyperphagia as well as progressive vision loss, deafness, cardiomegaly, insulin resistance and other signs and symptoms. Variable features include short stature, cardiomyopathy, and progressive lung, liver, and kidney dysfunction. Symptoms of Alström syndrome first appear in infancy, and progressive development of multi-organ pathology leads to a reduced life expectancy, with survival rare beyond the age of 50.

Alström syndrome shares many clinical features with BBS, including obesity and hyperphagia, and is also characterized by progressive vision loss, deafness, congestive heart failure, hyperinsulinemia and type 2 diabetes mellitus. Similarly, Alström syndrome is a ciliopathy caused by mutations in the *ALMS1* gene, which has also been shown to be important for cilia function. Like BBS, recent scientific studies identify genetic deficiencies affecting the MC4R signaling pathway as a potential cause of the obesity and hyperphagia associated with Alström syndrome. Studies in a mouse model of Alström syndrome show a reduction in the number of cilia in specific neurons in the hypothalamus that are critical for MC4R pathway signaling. While Alström syndrome is less well studied than BBS, the similar pathophysiology of cilia dysfunction and clinical presentation support that deficiencies in the MC4R pathway are implicated in the obesity and hyperphagia observed in Alström syndrome. Therefore, we hypothesize that setmelanotide treatment can be applied to treat Alström syndrome.

We are studying Alström syndrome patients who are severely obese. As stated above, our Phase 3 study included three patients with Alström syndrome in the primary analysis and none of them met the primary endpoint. However, there were signals of potential efficacy in some patients, and we are exploring further these phase 3 data. One pediatric patient with Alström syndrome lost 8 percent of body weight in the pivotal trial. In our Phase 2 trial, we had enrolled four patients with Alström syndrome. One of those patients, a 12-year-old male, lost 25 percent of body weight, and another patient who achieved and maintained 6 percent weight loss also saw her HbA1c decrease by 3 percent from 11 percent to 8 percent.

We are evaluating next steps for setmelanotide for the potential treatment of patients with Alström syndrome.

Community-building efforts for BBS and Alström Syndrome

The ongoing efforts outlined to support the POMC, PCSK1 and LEPR launch lay the foundation for future commercialization efforts, including potential for BBS and Alström if setmelanotide is ultimately approved in these indications. All disease education efforts supporting awareness of rare genetic diseases of obesity and testing will also uncover BBS and Alström patients. In addition, compared to POMC, PCSK1 and LEPR, BBS and Alström are syndromic diseases where patients suffer from multiple symptoms beyond early-onset obesity and hyperphagia. This allows for a tailored approach to disease education efforts to differentiate individuals with BBS and Alström syndrome from the broader general obese population.

Initial primary and secondary market research has been conducted to understand the patient journey to diagnosis and treatment and the HCPs involved in the diagnosis and management of individuals with BBS and Alström syndrome. This research demonstrates there is still a need to decrease the time to diagnosis and increase awareness of these diseases, particularly education around how the underlying pathology causing obesity in BBS and Alström Syndrome differs from common obesity. Currently HCPs often treat the obesity and hyperphagia with traditional obesity management practices that frequently prove insufficient, leading to inadequate improvements and frustration for diagnosed individuals. We continue to advance our education and community building efforts as we make progress against these unmet needs in the community through engagements with existing HCP treaters, diagnosers, referrers, along with patient advocacy groups.

We continue to hone our understanding of the number of diagnosed individuals, while supporting additional patient identification. An ongoing assessment of the market will guide decisions around future headcount needs to support the launch in BBS/AS, whether from a field perspective or to supplement our existing patients and customer support services.

Additional MC4R Pathway Genetic Deficiencies: HETs, SRC1 and SH2B1

We are actively working to broaden the indication for setmelanotide to treat individuals with additional genetic deficiencies related to the MC4R pathway through our clinical development program. We anticipate initiating a Phase 3, potentially registration-enabling study in the second half of 2021 to evaluate setmelanotide in patients with MC4R pathway deficiencies due to a variant in one of the two alleles in the POMC, PCSK1, or LEPR genes, or HET obesity, as well as the SRC1 and SH2B1 genes. In addition, we plan to initiate an expanded Phase 2 Basket Study to evaluate setmelanotide for the treatment of obesity due to a deficiency in one of 31 additional genes associated with the MC4R pathway.

POMC, PCSK1 or LEPR heterozygous deficiency obesity

POMC, PCSK1 and LEPR are core genes of the MC4R pathway. Heterozygous variants in POMC, PCSK1 and LEPR have been associated with clinical obesity that may be due to a MC4R pathway dysfunction. The epidemiology and clinical characterization POMC, PCSK1, or LEPR heterozygosity obesity, or HET obesity, is not well understood. We are studying patients who are severely obese and who carry a heterozygous variant of the POMC, LEPR, or PCSK1 gene. These patients have a genetic variant that may result in MC4R pathway dysfunction.

SRC1 deficiency obesity

SRC1 deficiency obesity is a rare genetic disorder that is characterized by early-onset severe obesity and hyperphagia. The first academic paper describing SRC1 deficiency obesity, titled, “Steroid receptor coactivator-1 modulates the function of POMC neurons and energy homeostasis” (Yang et al 2019, Nat Comm. 10, Article 1718) was published in 2019 in Nature Communications. In this paper, the authors described how SRC1 variants found in severely obese cases significantly impaired leptin-induced POMC expression. SRC1 deficiency obesity is an autosomal dominant disorder, meaning that heterozygote loss of the SRC1 gene (just one gene copy) can be sufficient to give rise to obesity and hyperphagia. Specifically, SRC1 is a transcriptional coactivator that has links to both the leptin receptor and to POMC. When the leptin receptor is activated, SRC1 through a cascade of events itself is activated and then goes on to drive the expression of POMC, such that in individuals who have heterozygote mutations in their SRC1 genes, there can be insufficient leptin receptor activation of the MC4 receptor pathway as a result of decreased POMC expression, which decreases the amount of available MSH to reactivate the MC4 receptor, consequentially resulting pathway dysfunction that drives the hyperphagia and obesity in these individuals.

SH2B1 deficiency obesity

SH2B1 deficiency obesity is a rare genetic disorder that is characterized by early-onset severe obesity, hyperphagia and hyperinsulinemia. In addition to early-onset severe obesity and hyperphagia, other clinical characteristics associated with SH2B1 deficiency obesity are insulin resistance and reduced final height. Deficiency in SH2B1 can arise through either DNA variants in the SH2B1 gene or through chromosomal deletions (chromosome 16) that encompass the SH2B1 gene. In both cases, dysfunction/loss of only one copy of the SH2B1 gene is sufficient to give rise to obesity and hyperphagia. The SH2B1 protein has been shown to have direct links to the MC4R-pathway. Specifically, SH2B1 is an adapter protein that amplifies the signal coming through the leptin receptor. In individuals who carry heterozygote loss of function mutations in SH2B1 or a chromosomal deletion that remove the SH2B1 from the chromosome, individuals may have insufficient leptin receptor activity activation of their MC4R pathway. This gives rise to a well-documented form of severe early-onset obesity and hyperphagia.

Proof of concept achieved in HET obesity and obesity due to SRC1 or SH2B1 deficiencies

Our ongoing Phase 2 Basket Study is an open label study designed to evaluate setmelanotide in obese patients whose Body Mass Index (BMI) $\geq$ 30 kg/m^2 for patients 16 years of age or older or BMI$\geq$ 95th percentile for age and gender for patients between 6 and 16 years old. Patients were stratified by cohort according to their genetic defect (i.e., HETs, SRC1 or SH2B1, or others). On Jan. 26, 2021, we announced proof-of-concept interim data from this study in HET obesity, obesity due to SRC1 deficiency; and obesity due to SH2B1 deficiency. 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, LEPR, PCSK1) highlights included, as of a cutoff of December 17, 2020:

- 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; and
- Among the 12 patients who achieved the primary endpoint (responder group), the mean reduction from baseline in body weight was -10.1 percent.

In our analyses, we are applying variant classification guidelines from the American College of Medical Genetics, or ACMG (as described in Richards, et al., 2015), to patient cohort stratification. Specific variants of the POMC, LEPR, PCSK1, SRC1 or SH2B1 gene may be classified based published data as being pathogenic, likely pathogenic, likely benign or benign, or classified as a variant of unknown significance or VOUS. As genetics of obesity remains an emerging field, the vast majority of variants in genes associated with the MC4R pathway as classified as VOUS. Our hypothesis was that patients with genetic variants that indicate a higher degree of pathogenicity would be more likely to have impaired pathway signaling and therefore more likely to respond to setmelanotide. In addition, we decided to study a cohort of patients with an N221D variant of the PCSK1 gene. This is a common variant which has been associated with obesity in scientific and medical literature.

- Patients with HET obesity were stratified into three pre-specified cohorts by classification of their genetic variants according to ACMG 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; and
- Four of 19 patients (21.1 percent) with a variant of unknown significance (VOUS) 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 remained on trial but had not yet reached 12 weeks of therapy as of December 17, 2020.

Obesity due to SRC1 deficiency highlights included, as of a cutoff date of December 17, 2020:

- 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; and
- 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 included, as of a cutoff date of December 17, 2020:

- 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; and

- 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 as of the cutoff date. The most common treatment-emergent adverse events, or TEAEs, included mild injection site reactions, hyperpigmentation, and nausea and vomiting, which occurred early in the treatment course. There were no SAEs 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.

MC4 Receptor Deficiency Obesity

In the first half of 2021, we anticipate reporting interim data from ongoing Phase 2 basket trial from a cohort of patients with MC4R deficiency obesity arising due to heterozygote loss of function mutations in the MC4 receptor gene itself. This is one of the most well-known and prevalent forms of monogenic severe early-onset obesity. Based on a comprehensive ongoing biochemical screening study, we believe setmelanotide may have the potential to address MC4R loss of function in a defined subset of this broader population, specifically individuals who carry MC4R loss of function variants that can be rescued by setmelanotide (e.g. are not responsive to the endogenous ligand MSH, but do respond normally to setmelanotide.

Smith-Magenis Syndrome

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

Additional Planned Phase 2 Studies

Expanded Phase 2 MC4R Pathway Basket Study

Leveraging our extensive scientific expertise and years of internal research, we have developed a process that allows us to identify new genes that we believe may be responsive to setmelanotide. Through this proprietary gene curation and selection strategy specifically designed to evaluate a gene's relevance to the MC4R pathway, we have identified an additional 31 MC4R pathway genes with "strong" or "very strong" pathway relevance, which we plan to evaluate in an expanded Phase 2 Basket Study. Similar to our ongoing exploratory Phase 2 Basket Study, we will look to enroll patients with early-onset, severe obesity with a body mass index (BMI) $\geq$40 kg/m^2 with a confirmed genetic variant of one of these 31 genes. We expect that patient identified for this study will be screened, stratified into cohorts by gene and receive setmelanotide therapy over 12 to 16 weeks. We expect to finalize this study design and initiate this trial in the second half of 2021.

Hypothalamic Obesity

Hypothalamic obesity, or HO, is a severe obesity that arises from mechanical hypothalamic insults. Lesions of the hypothalamus can derive from various types of tumors (e.g., craniopharyngiomas, gliomas, pituitary adenomas,

hamartomas) or may be caused by surgeries and radiotherapies for the treatment of these same tumor types. These hypothalamic lesions, whether caused by the tumor itself and/or the treatment of the tumor, can disrupt the MC4R pathway. Moreover, patients with HO display high degree of hyperleptinemia and hyperinsulinemia. Alpha-melanocortin stimulating hormone (MSH) can be detectable in blood, and its levels can change depending on different energy states; however, in patients with craniopharyngioma or post-surgical treatment for it, α-MSH levels are significantly reduced. Reduced serum α-MSH levels may suggest melanocortin pathway deficiency, which might explain obesity in these patients.

We plan to conduct a Phase 2, multi-center, open-label, proof of concept study designed to assess the effect of setmelanotide on weight loss on a population affected by HO. Approximately 15 subjects aged 6 to 28 years, inclusive, are planned to be enrolled across approximately 3-5 clinical sites in the United States. We expect that patients will be treated with setmelanotide for 16 weeks, with the primary endpoint being the percentage of subjects aged >12 years with ≥5 percent body weight loss from baseline compared to a historic control of <5 percent in this subject population. All enrolled patients will be obese, defined as a BMI ≥35 kg/m^2 for subjects ≥16 years of age or BMI ≥99th percentile for age and gender for subjects 6 to <16 years of age based on the U.S. Centers for Disease Control and Prevention criteria.

Weekly Formulation of Setmelanotide

In collaboration with Camurus AB, or Camurus, we have developed a once weekly, long-acting formulation using FluidCrystal® technology. When injected subcutaneously, aqueous body fluid is absorbed by the excipient lipid phase which forms a gel-like depot consisting of liquid crystals formed in situ leading to slow diffusion of setmelanotide from the depot. We believe that this formulation may be more convenient and less burdensome for patients and their families.

In November 2020, we presented interim results from a Phase 2 study evaluating a once-weekly formulation of setmelanotide in healthy obese volunteers. The data showed that, as of a cutoff date of April 17, 2020, healthy obese people treated with the weekly formulation of setmelanotide achieved comparable weight loss to those treated with the daily formulation and that both weekly and daily formulations of setmelanotide were observed to be generally well tolerated. A total of 85 individuals were included in the interim data analysis: 28 individuals were treated with weekly setmelanotide without titration for 12 weeks (10mg, 20mg or 30mg doses); 20 individuals were treated with weekly setmelanotide with titration (10mg for one week, followed by 20mg for 11 weeks or 20mg for one week, followed by 30mg for 11 weeks); 13 individuals were treated with daily setmelanotide (2mg daily for one week, followed by 3mg daily for 11 weeks); and 24 individuals were treated with placebo for 12 weeks.

We plan to discuss our development plans with the FDA and EMA in the first half of 2021 and anticipate dosing the first patient in our planned once-weekly clinical trial in late 2021.

These interim data showed that, as of the cutoff date of April 17, 2020, the weight and hunger score changes in individuals who received the weekly formulation were generally comparable to the score changes observed in individuals who received the daily formulation. Notably, the weight and hunger score changes in healthy obese individuals receiving both formulations were lower than those reported separately in patients with rare genetic obesities associated with an impaired MC4R pathway who received setmelanotide. We believe the interim results from this study reinforces the position that setmelanotide is a precision medicine targeted at patients with deficits in the MC4R pathway. Additionally, pharmacokinetic, or PK, analyses showed similar trough drug concentrations for the daily and weekly formulations over the duration of therapy. The weekly formulation of setmelanotide demonstrated a consistent 24-hour PK range and was detected steadily over one week, with a trough concentration consistent with the trough concentration of the daily formulation.

As of the data cutoff of April 17, 2020, weekly setmelanotide administration was generally well tolerated, with no serious TEAEs, and the safety results were similar to the daily administration and consistent with prior clinical experience. The most commonly reported TEAEs, rates of which were generally similar between individuals treated with the weekly and daily formulations, included injection site reaction, hyperpigmentation, nausea, headache and vomiting.

Safety and Tolerability Results

Historically, clinical data with other MC4R therapies suggested that MC4R-mediated side effects may include changes in blood pressure and heart rate, increased erections in males, changes in libido and sexual function in females and nausea and vomiting. As a result, primarily due to concerns about blood pressure and heart rate changes, we are not aware of any other MC4R agonists are currently in the clinic for the treatment of obesity and/or hyperphagia. It is noteworthy that the pattern of effects differed among each of the other MC4R therapies, underscoring the complex physiology of MC4R. With setmelanotide, there has been little, if any, evidence of blood pressure or heart rate changes, preliminarily supporting an important differentiation of setmelanotide from previous MC4R therapies. Monitoring for blood pressure and heart rate changes, as well as other potential AEs, is included in all setmelanotide clinical trials.

Because of these first generation MC4R therapy failures, the setmelanotide program employed an intensive preclinical screening program to assess clinical candidates for blood pressure and heart rate effects, along with efficacy. The cornerstone of this preclinical screening program was a significant investment in obese primate studies which validated setmelanotide as a promising compound for clinical development. More recently, new research supporting a unique mechanism of action of setmelanotide, compared to earlier MC4R agonists and the endogenous ligand MSH, was published in May 2018 in *Nature Medicine*.

Setmelanotide was generally well tolerated in our Phase 1, Phase 2 and Phase 3 clinical trials to date. Overall, except as outlined below, the number and patterns of AEs were generally low, and the intensity of the AEs was generally mild, and infrequently led to clinical trial discontinuation.

To evaluate whether setmelanotide has the potential to avoid adverse cardiovascular issues, we studied setmelanotide in obese primate preclinical studies, with special attention to cardiovascular effects. The results of these studies supported testing in clinical trials. In the clinical trials, we monitored blood pressure and heart rate extensively, primarily by 24-hour ambulatory blood pressure monitoring, or ABPM. In most clinical trials, there were multiple 24-hour ABPM periods, both on a pre-treatment and post-treatment basis. Trial-by-trial review of the 24-hour ABPM data showed little, if any, evidence of changes in heart rate and/or blood pressure even at the highest doses tested in Phase 1 and Phase 2 clinical trials. We have also conducted an analysis of 24-hour ABPMs that were obtained pre-dose and post-dose across completed studies, which was presented at the Obesity Society in 2015. This included 128 patients, of which 79 were active and 49 were on a placebo. Overall, there was little, if any, evidence of blood pressure or heart rate changes evident from baseline versus placebo in any trial, preliminarily supporting an important differentiation of setmelanotide from previous MC4R therapies.

In the majority of our trials, we observed a small increase in frequency of penile erections in male patients, as well as signs of sexual arousal in a small number of female patients. These symptoms were infrequent, generally mild, not painful, and short-lived. Most often these symptoms were reported in the first week of treatment. There was a small incidence of nausea and vomiting, as well as injection site reactions, both of which usually were reported as mild, early in treatment, and short-lived. A small number of patients had dose reductions and/or discontinued treatment due to nausea and vomiting.

We also noted darkening of skin and skin lesions, such as moles and freckles, in most patients who received setmelanotide. This was likely caused by activation of the closely related MC1 receptor, the receptor that mediates skin darkening in response to sun exposure. This was observed generally after one to two weeks of treatment, most often plateaued by two to four weeks of treatment, and like sun-related tanning, generally returned to baseline after cessation of exposure.

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

Life-Cycle Management and Preclinical Development

We continue to advance the development of our once-weekly formulation of setmelanotide for all indications in which setmelanotide is approved or in development. We plan to discuss our development plans with the FDA and EMA

in the first half of 2021 and anticipate dosing the first patient in our planned once-weekly clinical trial in late 2021. In addition, we have initiated development of an auto-injector device designed to make administration of our once-weekly product candidate easier and more convenient for our patients.

IMCIVREE is approved in the US for patients 6 years of age and older. We are also seeking approval for pediatric patients 6 years of age and older in the EU. We have identified children with genetic obesity under 6 years of age who we believe may potentially benefit from treatment with setmelanotide. We plan to initiate a clinical study in POMC deficiency obesity, LEPR deficiency obesity, and BBS patients 2 – 5 years of age in the second half of 2021. In addition, we have initiated discussions with the EMA to modify our EMA-approved Pediatric Investigation Plan, or PIP, to be consistent with our plans for the treatment of these younger patients. We expect to meet all our PIP requirements by 2024.

We are no longer pursuing development of a pre-clinical asset, RM-853, a ghrelin O acyltransferase inhibitor that had been in preclinical development for Prader-Willi syndrome, a rare genetic disorder that results in hyperphagia and early-onset, life-threatening obesity.

We have initiated a program to identify next generation MC4R agonists based on the setmelanotide chemical space that both have the potential to avoid cardiovascular AEs and MC1R activation, the latter of which results in hyperpigmentation. This program is expected to result in a clinical development candidate that will be a potent MC4R agonist matching setmelanotide's cardiovascular safety but without the potential to cause hyperpigmentation. We expect to identify a lead compound from this program for preclinical development in 2022.

Genetic Sequencing and Patient Finding

We continue to expand our sequencing efforts in individuals living with early-onset, severe obesity to support research, patient finding and community building efforts in order to better understand rare genetic diseases of obesity. Our obesity DNA database contains sequencing samples from approximately 37,500 individuals, and we are using these data to support research, patient finding and community building while forging a better understanding of rare genetic diseases of obesity. With our focus on the MC4R pathway, we believe this database is an important resource for identifying new indications for clinical development with new populations and prevalence estimates for who may benefit from setmelanotide. By bringing additional awareness to these rare genetic diseases of obesity, our sequencing efforts have the potential to help foster patient communities and drive medical action in these populations.

We analyze these samples utilizing a proprietary gene curation and selection strategy to assess each gene's relevance to the MC4R pathway. For example, we used this approach in identifying the 31 additional MC4R pathway genes that we plan to evaluate in our expanded Phase 2 Basket Study.

Our sequencing data comes from three sources:

Uncovering Rare Obesity

As severe obesity is epidemic in the United States, we are focused on identifying people with early-onset obesity that may be caused by certain rare genetic variants. As part of these efforts, we have launched Uncovering Rare Obesity in order to increase access to genetic testing. As of December 31, 2020, 2,035 United States health care providers have requested 13,900 Uncovering Rare Obesity kits, and 6,163 sequencing tests have been ordered and patient samples collected. We launched the program in summer 2019, and we did experience a decrease in ordered and processed kits in 2020 due to the COVID-19 pandemic, as many people stayed away from health care facilities. Moving forward, we expect that Uncovering Rare Obesity, or URO, our free genetic testing program designed to help determine if individuals have an underlying genetic cause of their severe obesity, will become the primary driver of how we collect sequencing samples and identify patients.

This program complements several initiatives designed to advance the understanding of genetic causes of severe obesity, and Uncovering Rare Obesity broadens these efforts and brings access to genetic testing into the community setting. Currently available physician-ordered genetic testing panels are often cost prohibitive, while many consumer

genetic tests are incomplete when it comes to genetic disorders of obesity. This makes it difficult to confirm an underlying genetic cause of severe obesity. We believe the program marks an important step in the understanding of these disorders that might help patients and their families find new diagnosis and treatment strategies in the years ahead.

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

Genotyping Study

We have completed our initial genotyping study—the Genetic Obesity ID | Genotyping Study, with approximately 10,000 patients having been enrolled in the study. We included approximately 100 genes which, in medical and scientific literature, have been associated with obesity, including other genes associated with the MC4R pathway. We genotyped patients who entered the study through one of three arms including: a history of early-onset, severe obesity, and hyperphagia, high BMI, and individuals within three months of bariatric surgery. We plan to work with these investigators to publish the results of this study and guidance on the use of the algorithm for screening, to enable more systematic diagnoses of these rare genetic disorders of obesity.

Biobanks

The third source of our sequencing data come from global network of collaborations with obesity researchers we built over time with treaters and the biggest institutes that generate large quantities of DNA sequence data. Biobank based sequencing provides data principally for scientific and epidemiological research.

Competition

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

Currently, IMCIVREE is the only approved treatment for regulating hunger and hyperphagia related behaviors of patients with obesity due to POMC, PCSK1 or LEPR deficiencies, and there are no approved treatments for regulating hunger and hyperphagia related behaviors of patients BBS, Alström syndrome, POMC heterozygous deficiency obesity, SRC1 deficiency obesity, SH2B1 deficiency obesity, MC4R deficiency obesity, or Smith-Magenis syndrome. Bariatric surgery is not a treatment option for these genetic diseases of obesity because the severe obesity and hyperphagia associated with these diseases are considered to be risk factors for bariatric surgery.

Licensing Agreements

Ipsen Pharma S.A.S.

Pursuant to a license agreement with Ipsen Pharma S.A.S., or Ipsen, we have an exclusive, sublicensable, worldwide license to certain patents and other intellectual property rights to research, develop, and commercialize compounds that were discovered or researched by Ipsen in the course of conducting its MC4R program or that otherwise were covered by the licensed patents. Rights under the license included the right to research, develop and commercialize setmelanotide. Pursuant to the license, we have a non-exclusive, sublicensable, worldwide license to certain patents and

other intellectual property rights that were licensed by Ipsen from a third party or that Ipsen may develop in the future to research, develop, and commercialize any of the compounds exclusively licensed by Ipsen pursuant to the license.

Under the terms of the Ipsen license agreement, Ipsen is eligible to receive payments of up to $40.0 million upon the achievement of certain development and commercial milestones in connection with the development, regulatory approval and commercialization of applicable licensed products, and royalties on future sales of the licensed products. Substantially all of the aggregate payments under the Ipsen license agreement are for milestones that may be achieved no earlier than first commercial sale of the applicable licensed product, and to date, we have paid $4.0 million in clinical and regulatory milestones. Royalties in the mid-single digits on future sales of the applicable licensed products will be due under the Ipsen license agreement on a licensed product-by-licensed product and country-by-country basis until the later of the date when sales of a licensed product in a particular country are no longer covered by patent rights licensed pursuant to the Ipsen license agreement and the tenth anniversary of the date of the first commercial sale of the applicable licensed product in the applicable country. The term of the Ipsen license agreement continues until the expiration of the applicable royalty term on a country-by-country and product-by- product basis. Upon expiration of the term of the agreement, the licensed rights granted to us under the agreement, to the extent they remain in effect at the time of expiration, will thereafter become irrevocable, perpetual and fully paid-up licenses that survive the expiration of the term. We have a right to terminate the license agreement at any time during the term for any reason on 180 days' written notice to Ipsen. Ipsen has a right to terminate the agreement prior to expiration of its term for our material breach of the agreement, our failure to initiate or complete development of a licensed product or our bringing an action seeking to have an Ipsen license patent right declared invalid. Upon any early termination of the license agreement not due to Ipsen's material breach, all licensed rights granted under the license agreement will terminate.

Camurus

In January 2016, we entered into a license agreement for the use of Camurus' drug delivery technology, FluidCrystal, to formulate setmelanotide with Camurus. Under the terms of the agreement, Camurus granted us a worldwide license to the FluidCrystal technology to formulate setmelanotide and to develop, manufacture, and commercialize this new formulation for once-weekly dosing, administered as a SC injection. The license granted to us is specific to the FluidCrystal technology incorporating setmelanotide. Under the terms of the license agreement, we are responsible for manufacturing, development, and commercialization of the setmelanotide FluidCrystal formulation worldwide. Camurus received a non-refundable and non-creditable upfront payment of $0.5 million in January 2016, and is eligible to receive progressive payments of approximately $65.0 million, of which the majority are sales milestones. In addition, Camurus is eligible to receive tiered, mid to mid-high, single digit royalties on future sales of the product.

The term of the agreement continues until the expiration of the applicable royalty term on a country-by-country and product-by-product basis. Upon expiration of the term of the agreement, the licensed rights granted to us under the agreement, to the extent they remain in effect at the time of expiration, will thereafter become irrevocable, perpetual and fully paid-up licenses that survive the expiration of the term. We have a right to terminate the license agreement at any time during the term for any reason upon 90 days' written notice to Camurus. Camurus has a right to terminate the agreement prior to expiration of its term for our material breach of the agreement, if we voluntarily or involuntarily file for bankruptcy, or for our bringing an action seeking to have a Camurus license patent right declared invalid. Upon any early termination of the license agreement not due to Camurus' material breach, all licensed rights granted under the license agreement will terminate.

Takeda

In March 2018, we acquired exclusive, worldwide rights from Takeda to develop and commercialize RM-853. RM-853 is a potent, orally available GOAT inhibitor currently in preclinical development for Prader-Willi Syndrome, or PWS. PWS is a rare genetic disorder that results in hyperphagia and early-onset, life-threatening obesity, for which there are no approved therapeutic options. We will assume sole responsibility for the global product development and commercialization of RM-853. Takeda received an upfront fee of $4.4 million which we settled in April 2018 with shares of our common stock, and is eligible to receive milestone payments of approximately $140.0 million, most of which are payable upon regulatory approval or are sales milestones. In addition, Takeda is eligible to receive back-end development milestones, and single-digit royalties on future RM-853 sales.

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

The term of the agreement continues until the expiration of the applicable royalty term on a country-by-country and product-by-product basis. Upon expiration of the term of the agreement, the licensed rights granted to us under the agreement, to the extent they remain in effect at the time of expiration, will thereafter become irrevocable, perpetual and fully paid-up licenses that survive the expiration of the term. We have a right to terminate the license agreement at any time during the term for any reason upon 90 days' written notice to Takeda. Takeda has a right to terminate the agreement prior to expiration of its term for our material breach of the agreement, if we voluntarily or involuntarily file for bankruptcy, or for our bringing an action seeking to have a Takeda license patent right declared invalid. Upon any early termination of the license agreement not due to Takeda's material breach, all licensed rights granted under the license agreement will terminate.

Patents and Proprietary Rights

We have in-licensed a large patent portfolio from Ipsen for our melanocortin programs. The portfolio includes multiple patent families, and all of these in-licensed patent families are being prosecuted or maintained by Ipsen in consultation with us. We have also filed patent applications in six families which are exclusively owned and maintained by us that relate to the melanocortin program.

Our MC4R portfolio of licensed and exclusively owned patent families, which includes setmelanotide, consists of 13 patent families currently being prosecuted or maintained, which include applications and patents directed to compositions of matter, formulations and methods of treatment using setmelanotide. As of December 31, 2020, the portfolio for the MC4 program consists of 14 issued United States patents and 228 issued non-United States patents across 8 of the 13 families. There also 13 pending United States patent applications and 76 pending non-United States applications in 24 jurisdictions.

In the patent family directed to selected MC4R receptor agonists, including the composition of matter for setmelanotide, we have 3 issued United States patents and 108 issued non-United States patents, including Australia, Canada, China, Europe, Hong Kong, India, Israel, Japan, Korea, New Zealand, Russia and Singapore. The standard 20-year term for patents in this family would expire in 2026, but two of the United States patents are expected to expire in 2027 due to patent term adjustments. Patent term extensions for delays in marketing approval may also extend the terms of patents in this family, and we have filed for patent term extension in the United States that, if granted, would extend the composition of matter patent protection to 2032.

In addition to the patents and patent applications discussed above, we co-own one patent family with Charité-Universitätsmedizin Berlin, which has been filed in 21 jurisdictions. We also co-own one patent family with the University of Strasbourg and the French National Institute of Health and Medical Research, which has been filed in 4 jurisdictions. Both of these patent families relate to the melanocortin program.

We have also in-licensed a patent family from Takeda directed to the composition of matter and methods of use of ghrelin O-acetyltransferase inhibitors, including RM-853. This patent family includes 1 issued United States patent, nine issued non-United States patents including China, Europe, and Japan, and one allowed application in Canada. The standard 20-year term for the patents in this family will expire in 2033, though patent term extensions for delays in marketing approval may also extend the terms of patents in this family.

Intellectual Property Protection Strategy

We currently seek, and intend to continue seeking, patent protection whenever commercially reasonable for any patentable aspects of setmelanotide and related technology or any new products or product candidates we acquire in the future. Where our intellectual property is not protected by patents, we may seek to protect it through other means, including

maintenance of trade secrets and careful protection of our proprietary information. Our license from Ipsen for the melanocortin program require Ipsen, subject to certain exceptions and upon consultation with us, to prosecute and maintain its patent rights as they relate to the licensed compounds and methods. If Ipsen decides to cease prosecution or maintenance of any of the licensed patent rights, we have the option to take over prosecution and maintenance of those patents and Ipsen will assign to us all of its rights in such patents. For those patent rights that we own exclusively, we control all prosecution and maintenance activities.

The patent positions of biopharmaceutical companies are generally uncertain and involve complex legal, scientific and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Consequently, we do not know whether the product candidate we in-license will be protectable or remain protected by enforceable patents. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction, and furthermore, we cannot determine whether the claims of any issued patents will provide sufficient proprietary protection to protect us from competitors, or will be challenged, circumvented or invalidated by third parties. Because patent applications in the United States and certain other jurisdictions are maintained in secrecy for 18 months, and since publication of discoveries in the scientific or patent literature often lags behind actual discoveries, we cannot be certain of the priority of inventions covered by pending patent applications. This potential issue is exacerbated by the fact that, prior to March 16, 2013, in the United States, the first to make the claimed invention may be entitled to the patent. On March 16, 2013, the United States transitioned to a "first to file" system in which the first inventor to file a patent application may be entitled to the patent. For applications filed prior to the institution of the "first to file" system, we may have to participate in interference proceedings declared by the United States Patent and Trademark Office, or PTO, or a foreign patent office to determine priority of invention. Moreover, we may have to participate in other proceedings declared by the United States PTO or a foreign patent office, such as post-grant proceedings and oppositions, that challenge the validity of a granted patent. Such proceedings could result in substantial cost, even if the eventual outcome is favorable to us.

Although we currently have issued patents directed to a number of different attributes of our products, and pending applications on others, there can be no assurance that any issued patents would be held valid by a court of competent jurisdiction. An adverse outcome could subject us to significant liabilities to third parties, require disputed rights to be licensed from third parties or require us to cease using specific compounds or technology. To the extent prudent, we intend to bring litigation against third parties that we believe are infringing our patents.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the earliest date of filing a non-provisional patent application. In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the United States PTO in granting a patent, or may be shortened if a patent is terminally disclaimed over another patent with an earlier expiration date.

As mentioned above, in the United States, the patent term of a patent that covers an FDA-approved drug may also be eligible for patent term extension, which permits patent term restoration as compensation for the patent term lost during the FDA regulatory review process. Setmelanotide has received FDA approval and we have filed for patent term extension on that product. In the future, if and when our other pharmaceutical products receive FDA approval, we expect to apply for patent term extensions on patents covering those products. We intend to seek patent term adjustments and extensions to any of our issued patents in any jurisdiction where these are available, however there is no guarantee that the applicable authorities, including the FDA in the United States, will agree with our assessment of whether such extensions should be granted, and even if granted, the length of such adjustments or extensions.

To protect our rights to any of our issued patents and proprietary information, we may need to litigate against infringing third parties, or avail ourselves of the courts or participate in hearings to determine the scope and validity of those patents or other proprietary rights. These types of proceedings are often costly and could be very time-consuming to us, and we cannot be certain that the deciding authorities will rule in our favor. An unfavorable decision could result in the invalidation or a limitation in the scope of our patents or forfeiture of the rights associated with our patents or pending patent applications. Any such decision could result in our key technologies not being protectable, allowing third parties to use our technology without being required to pay us licensing fees or may compel us to license needed technologies from third parties to avoid infringing third-party patent and proprietary rights. Such a decision could even result in the

invalidation or a limitation in the scope of our patents or could cause us to lose our rights under existing issued patents or not to have rights granted under our pending patent applications.

In addition, we intend to seek orphan drug exclusivity in jurisdictions in which it is available. A prerequisite to orphan drug exclusivity in the United States and in the European Union is orphan drug designation. An orphan drug designation may be granted, subject to fulfillment of specific criteria, where a drug is developed specifically to treat a rare or uncommon medical treatment. If a product which has an orphan drug designation subsequently receives the first regulatory approval for the indication for which it has such designation, the product is entitled to orphan exclusivity, meaning that the applicable regulatory authority may not approve any other applications to market the same drug for the same indication, except in certain very limited circumstances, for a period of seven years in the United States and 10 years in the European Union. Orphan drug exclusivity does not prevent competitors from developing or marketing different drugs for an indication. We have received orphan drug designation in the United States for the use of setmelanotide for five indications and approval for two of those indications.

We also rely on trade secret protection for our confidential and proprietary information. Although we take steps to protect our proprietary information and trade secrets, including through contractual means with our employees and consultants, no assurance can be given that others will not independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets or disclose such technology, or that we can meaningfully protect our trade secrets. It is our policy to require our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors to execute confidentiality agreements upon the commencement of employment or consulting relationships with us. These agreements provide that all confidential information developed or made known to the individual during the course of the individual's relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances. In the case of employees, the agreements provide that all inventions conceived by the individual will be our exclusive property. There can be no assurance, however, that these agreements will provide meaningful protection or adequate remedies for our trade secrets in the event of unauthorized use or disclosure of such information.

Manufacturing

We currently contract with various third parties for the manufacture of setmelanotide and intend to continue to do so in the future. We have entered into process development and manufacturing service agreements with our CMOs, Corden Pharma Brussels S.A, or Corden (formerly Peptisyntha SA prior to its acquisition by Corden), PolyPeptide Group, Baine L'Alleud, or Polypeptide, Neuland Laboratories, and Recipharm Monts S.A.S for certain process development and manufacturing services for regulatory starting materials and/or drug substance, or API, and drug product in connection with the manufacture of setmelanotide. Under our agreements, we pay these third parties for services in accordance with the terms of mutually agreed upon work orders, which we may enter into from time to time. We may need to engage additional third-party suppliers to manufacture our clinical and commercial drug supplies. In connection with our commercialization of setmelanotide or any future product candidate, we have engaged and will need to engage other third parties to assist in, among other things, labeling, packaging and distribution. Under the current agreements, each party is subject to customary indemnification provisions.

Our contract manufacturing agreements give us visibility into the expected future cost of producing setmelanotide at commercial scale. Based upon a range of prices of currently-marketed therapies indicated for orphan diseases, we believe that our cost of goods for setmelanotide will be highly competitive.

We currently have no plans to build our own clinical or commercial scale manufacturing capabilities. To meet our projected needs for clinical supplies to support our activities through regulatory approval and commercial manufacturing, the CMOs with whom we currently work may need to increase scale of production or we expect that we may need to secure alternate suppliers. We have not currently identified alternate suppliers in the event the current CMOs we utilize are unable to scale production. Because we rely on these CMOs, we have personnel with pharmaceutical development and manufacturing experience who are responsible for maintaining our CMO relationships.

Regulatory Matters

Government Regulation

Government authorities in the United States, at the federal, state and local level, and other countries extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, marketing and export and import of drug products. A new drug must be approved by the FDA through the NDA process before it may be legally marketed in the United States. We, along with any third-party contractors, will be required to navigate the various preclinical, clinical and commercial approval requirements of the governing regulatory agencies of the countries in which we wish to conduct studies or seek approval of our products and product candidates. The process of obtaining regulatory approvals and the subsequent compliance with applicable federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources.

U.S. Drug Development Process

In the United States, the FDA regulates drugs under the federal Food, Drug, and Cosmetic Act (FDCA) and its implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources. The process required by the FDA before a drug may be marketed in the United States generally involves the following:

- completion of preclinical laboratory tests, animal studies and formulation studies in accordance with FDA's Good Laboratory Practice requirements and other applicable regulations;
- submission to the FDA of an Investigational New Drug Application (IND), which must become effective before human clinical trials may begin;
- approval by an independent Institutional Review Board (IRB) or ethics committee at each clinical site before each trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practices (GCPs), to establish the safety and efficacy of the proposed drug for its intended use;
- preparation of and submission to the FDA of an NDA after completion of all pivotal trials;
- a determination by the FDA within 60 days of its receipt of an NDA to file the application for review
- satisfactory completion of an FDA advisory committee review, if applicable;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the drug is produced to assess compliance with current Good Manufacturing Practice (cGMP) requirements to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity, and of selected clinical investigation sites to assess compliance with GCPs; and
- FDA review and approval of the NDA to permit commercial marketing of the product for particular indications for use in the United States.

Prior to beginning the first clinical trial with a product candidate in the United States, a sponsor must submit an IND to the FDA. An IND is a request for authorization from the FDA to administer an investigational new drug product to humans. The central focus of an IND submission is on the general investigational plan and the protocol(s) for clinical studies. The IND also includes results of animal and *in vitro* studies assessing the toxicology, pharmacokinetics, pharmacology, and pharmacodynamic characteristics of the product; chemistry, manufacturing, and controls information; and any available human data or literature to support the use of the investigational product. An IND must become effective

before human clinical trials may begin. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30- day time period, raises safety concerns or questions about the proposed clinical trial. In such a case, the IND may be placed on clinical hold and the IND sponsor and the FDA must resolve any outstanding concerns or questions before the clinical trial can begin. Submission of an IND therefore may or may not result in FDA authorization to begin a clinical trial.

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical study. Clinical trials are conducted under protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A separate submission to the existing IND must be made for each successive clinical trial conducted during product development and for any subsequent protocol amendments. Furthermore, an independent IRB for each site proposing to conduct the clinical trial must review and approve the plan for any clinical trial and its informed consent form before the clinical trial begins at that site and must monitor the study until completed. Some studies also include oversight by an independent group of qualified experts organized by the clinical study sponsor, known as a data safety monitoring board, which provides authorization for whether or not a study may move forward at designated check points based on access to certain data from the study and may halt the clinical trial if it determines that there is an unacceptable safety risk for subjects or other grounds, such as no demonstration of efficacy. Depending on its charter, this group may determine whether a trial may move forward at designated check points based on access to certain data from the trial. The FDA or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. There are also requirements governing the reporting of ongoing clinical studies and clinical study results to public registries.

Human clinical trials are typically conducted in three sequential phases that may overlap or be combined:

- Phase 1: The product candidate is initially introduced into healthy human subjects or patients with the target disease or condition. These studies are designed to test the safety, dosage tolerance, absorption, metabolism and distribution of the investigational product in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness.

- Phase 2: The product candidate is administered to a limited patient population with a specified disease or condition to evaluate the preliminary efficacy, optimal dosages and dosing schedule and to identify possible adverse side effects and safety risks. Multiple Phase 2 clinical trials may be conducted to obtain information prior to beginning larger and more expensive Phase 3 clinical trials.

- Phase 3: The product candidate is administered to an expanded patient population to further evaluate dosage, to provide statistically significant evidence of clinical efficacy and to further test for safety, generally at multiple geographically dispersed clinical trial sites. These clinical trials are intended to establish the overall risk/benefit ratio of the investigational product and to provide an adequate basis for product approval.

In some cases, the FDA may require, or sponsors may voluntarily pursue, additional clinical trials after a product is approved to gain more information about the product. These so-called Phase 4 studies, may be conducted after initial marketing approval, and may be used to gain additional experience from the treatment of patients in the intended therapeutic indication. In certain instances, the FDA may mandate the performance of Phase 4 clinical trials as a condition of approval of an NDA.

Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug and finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the manufacturer must develop methods for testing the identity, strength, quality and purity of the final drug. In addition, appropriate packaging must be

selected and tested, and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

While the IND is active and before approval, progress reports summarizing the results of the clinical trials and nonclinical studies performed since the last progress report must be submitted at least annually to the FDA, and written IND safety reports must be submitted to the FDA and investigators for serious and unexpected suspected adverse events, findings from other studies suggesting a significant risk to humans exposed to the same or similar drugs, findings from animal or *in vitro* testing suggesting a significant risk to humans, and any clinically important increased incidence of a serious suspected adverse reaction compared to that listed in the protocol or investigator brochure.

In addition, during the development of a new drug, sponsors are given opportunities to meet with the FDA at certain points. These points may be prior to submission of an IND, at the end of Phase 2, and before an NDA is submitted. Meetings at other times may be requested. These meetings can provide an opportunity for the sponsor to share information about the data gathered to date, for the FDA to provide advice, and for the sponsor and the FDA to reach agreement on the next phase of development. Sponsors typically use the meetings at the end of the Phase 2 trial to discuss Phase 2 clinical results and present plans for the pivotal Phase 3 clinical trials that they believe will support approval of the new drug.

U.S. Review and Approval Process

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, the results of product development, preclinical and other non-clinical studies and clinical trials, along with descriptions of the manufacturing process, analytical tests conducted on the chemistry of the drug, proposed labeling and other relevant information are submitted to the FDA as part of an NDA requesting approval to market the product. Data can come from company-sponsored clinical studies intended to test the safety and effectiveness of a use of the product, or from a number of alternative sources, including studies initiated by independent investigators. The submission of an NDA is subject to the payment of substantial user fees; a waiver of such fees may be obtained under certain limited circumstances. Additionally, no user fees are assessed on NDAs for products designated as orphan drugs, unless the product also includes a non-orphan indication.

The FDA conducts a preliminary review of all NDAs within the first 60 days after submission, before accepting them for filing, to determine whether they are sufficiently complete to permit substantive review The FDA may request additional information rather than accept an NDA for filing. In this event, the NDA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing. Once filed, the FDA reviews an NDA to determine, among other things, whether a product is safe and effective for its intended use and whether its manufacturing is cGMP-compliant to assure and preserve the product's identity, strength, quality and purity. Under the Prescription Drug User Fee Act (PDUFA) guidelines that are currently in effect, the FDA has a goal of ten months from the filing date to complete a standard review of an NDA for a drug that is a new molecular entity. This review typically takes twelve months from the date the NDA is submitted to FDA because the FDA has approximately two months to make a "filing" decision after it the application is submitted.

The FDA may refer an application for a novel drug to an advisory committee. An advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA, the FDA will typically inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP and adequate to assure consistent production of the product within required specifications. Additionally, before approving a NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCPs. If the FDA determines that the application, manufacturing process or manufacturing facilities are not acceptable, it will outline the deficiencies in the submission and often will request additional testing or information. Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

After the FDA evaluates an NDA and conducts inspections of manufacturing facilities where the investigational product and/or its drug substance will be produced, the FDA may issue an approval letter or a Complete Response Letter (CRL). An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A CRL will describe all of the deficiencies that the FDA has identified in the NDA, except that where the FDA determines that the data supporting the application are inadequate to support approval, the FDA may issue the CRL without first conducting required inspections and/or reviewing proposed labeling. In issuing the CRL, the FDA may recommend actions that the applicant might take to place the NDA in condition for approval, including requests for additional information or clarification. The FDA may delay or refuse approval of an NDA if applicable regulatory criteria are not satisfied, require additional testing or information and/or require post-marketing testing and surveillance to monitor safety or efficacy of a product.

If regulatory approval of a product is granted, such approval will be granted for particular indications and may entail limitations on the indicated uses for which such product may be marketed. For example, the FDA may approve the NDA with a Risk Evaluation and Mitigation Strategy (REMS) to ensure the benefits of the product outweigh its risks. A REMS is a safety strategy to manage a known or potential serious risk associated with a medicine and to enable patients to have continued access to such medicines by managing their safe use, and could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries, and other risk minimization tools. The FDA also may condition approval on, among other things, changes to proposed labeling or the development of adequate controls and specifications. The FDA may also require one or more Phase 4 post- market studies and surveillance to further assess and monitor the product's safety and effectiveness after commercialization, and may limit further marketing of the product based on the results of these post-marketing studies.

In addition, the Pediatric Research Equity Act (PREA) requires a sponsor to conduct pediatric clinical trials for most drugs, for a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration. Under PREA, original NDAs and supplements must contain a pediatric assessment unless the sponsor has received a deferral or waiver. The required assessment must evaluate the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations and support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The sponsor or FDA may request a deferral of pediatric clinical trials for some or all of the pediatric subpopulations. A deferral may be granted for several reasons, including a finding that the drug is ready for approval for use in adults before pediatric clinical trials are complete or that additional safety or effectiveness data needs to be collected before the pediatric clinical trials begin. The FDA must send a non-compliance letter to any sponsor that fails to submit the required assessment, keep a deferral current or fails to submit a request for approval of a pediatric formulation.

Expedited Development and Review Programs

The FDA offers a number of expedited development and review programs for qualifying product candidates. For example, the Fast Track program is intended to expedite or facilitate the process for reviewing new products that are intended to treat a serious or life-threatening disease or condition and demonstrate the potential to address unmet medical needs for the disease or condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a fast track product has opportunities for more frequent interactions with the applicable FDA review team during product development and, once an NDA is submitted, the product candidate may be eligible for priority review. A Fast Track product may also be eligible for rolling review, where the FDA may consider for review sections of the NDA on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the NDA, the FDA agrees to accept sections of the NDA and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the NDA.

A product candidate intended to treat a serious or life-threatening disease or condition may also be eligible for Breakthrough Therapy designation to expedite its development and review. A product candidate can receive Breakthrough Therapy designation if preliminary clinical evidence indicates that the product candidate, alone or in combination with one or more other drugs or biologics, may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The designation includes all of the Fast Track program features, as well as more intensive FDA interaction and guidance

beginning as early as Phase 1 and an organizational commitment to expedite the development and review of the product candidate, including involvement of senior managers.

Any marketing application for a drug submitted to the FDA for approval, including a product candidate with a Fast Track designation and/or Breakthrough Therapy designation, may be eligible for other types of FDA programs intended to expedite the FDA review and approval process, such as priority review and accelerated approval. A product candidate is eligible for priority review if it is designed to treat a serious or life-threatening disease or condition, and if approved, would provide a significant improvement in safety or effectiveness compared to available alternatives for such disease or condition. For new-molecular-entity NDAs, priority review designation means the FDA's goal is to take action on the marketing application within six months of the 60-day filing date.

Additionally, product candidates studied for their safety and effectiveness in treating serious or life-threatening diseases or conditions may receive accelerated approval upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. As a condition of accelerated approval, the FDA will generally require the sponsor to perform adequate and well-controlled post-marketing clinical studies to verify and describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit. Products receiving accelerated approval may be subject to expedited withdrawal procedures if the sponsor fails to conduct the required post-marketing studies or if such studies fail to verify the predicted clinical benefit. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product.

Fast Track designation, Breakthrough Therapy designation, priority review, and accelerated approval do not change the standards for approval, but may expedite the development or approval process. Even if a product candidate qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

Orphan Drug Designation and Exclusivity

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug intended to treat a rare disease or condition, defined as a disease or condition with a patient population of fewer than 200,000 individuals in the United States, or a patient population greater than 200,000 individuals in the United States and when there is no reasonable expectation that the cost of developing and making available the drug in the United States will be recovered from sales in the United States for that drug. Orphan drug designation must be requested before submitting an NDA. After the FDA grants orphan drug designation, the generic identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA.

If a product that has orphan drug designation subsequently receives the first FDA approval for a particular active ingredient for the disease for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications, including a full NDA, to market the same drug for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity or if the FDA finds that the holder of the orphan drug exclusivity has not shown that it can assure the availability of sufficient quantities of the orphan drug to meet the needs of patients with the disease or condition for which the drug was designated. Orphan drug exclusivity does not prevent the FDA from approving a different drug for the same disease or condition, or the same drug for a different disease or condition. Among the other benefits of orphan drug designation are tax credits for certain research and a waiver of the NDA application user fee.

A designated orphan drug many not receive orphan drug exclusivity if it is approved for a use that is broader than the indication for which it received orphan designation. In addition, orphan drug exclusive marketing rights in the United States may be lost if the FDA later determines that the request for designation was materially defective or, as noted above, if a second applicant demonstrates that its product is clinically superior to the approved product with orphan exclusivity or the manufacturer of the approved product is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition.

Rare Pediatric Disease Priority Review Voucher Program

In 2012, Congress authorized the FDA to award priority review vouchers to sponsors of certain rare pediatric disease product applications. This program is designed to encourage development of new drug and biological products for prevention and treatment of certain rare pediatric diseases. Specifically, under this program, a sponsor who receives an approval for a drug or biologic for a "rare pediatric disease" may qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product. The sponsor of a rare pediatric disease drug product receiving a priority review voucher may transfer (including by sale) the voucher to another sponsor. The voucher may be further transferred any number of times before the voucher is used, as long as the sponsor making the transfer has not yet submitted the application. The FDA may also revoke any priority review voucher if the rare pediatric disease drug for which the voucher was awarded is not marketed in the U.S. within one year following the date of approval.

For purposes of this program, a "rare pediatric disease" is a (a) serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents; and (b) rare diseases or conditions within the meaning of the Orphan Drug Act. Congress has only authorized the Rare Pediatric Disease Priority Review Voucher program until September 30, 2024. Consequently, sponsors of marketing applications approved after that date will not receive the voucher unless Congress reauthorizes the Rare Pediatric Disease Priority Review Voucher program before that time. However, even if the program is not reauthorized, if a drug candidate receives Rare Pediatric Disease Designation before October 1, 2024, the sponsor of the marketing application for such drug will be eligible to receive a voucher if the application for the designated drug is approved by the FDA before October 1, 2026.

Post-approval Requirements

Drug products manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to record-keeping, reporting of adverse experiences, periodic reporting, product sampling and distribution, and advertising and promotion of the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing, annual program fees for any marketed products. Drug manufacturers and their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP, which impose certain procedural and documentation requirements upon us and our third-party manufacturers. Changes to the manufacturing process are strictly regulated, and, depending on the significance of the change, may require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting requirements. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMP and other aspects of regulatory compliance.

The FDA may withdraw approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical studies to assess new safety risks; or imposition of distribution restrictions or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters, or untitled letters;
- clinical holds on clinical studies;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of product approvals;

- product seizure or detention, or refusal to permit the import or export of products;
- consent decrees, corporate integrity agreements, debarment or exclusion from federal healthcare programs;
- mandated modification of promotional materials and labeling and the issuance of corrective information;
- the issuance of safety alerts, Dear Healthcare Provider letters, press releases and other communications containing warnings or other safety information about the product; or
- injunctions or the imposition of civil or criminal penalties.

The FDA closely regulates the marketing, labeling, advertising and promotion of drug products. A company can make only those claims relating to safety and efficacy, purity and potency that are approved by the FDA and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses. Failure to comply with these requirements can result in, among other things, adverse publicity, warning letters, corrective advertising and potential civil and criminal penalties. Physicians may prescribe, in their independent professional medical judgment, legally available products for uses that are not described in the product's labeling and that differ from those tested by us and approved by the FDA. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, restrict manufacturer's communications on the subject of off-label use of their products. However, companies may share truthful and not misleading information that is otherwise consistent with a product's FDA-approved labelling.

Marketing Exclusivity

Market exclusivity provisions authorized under the FDCA can delay the submission or the approval of certain marketing applications. The FDCA provides a five-year period of non-patent marketing exclusivity within the United States to the first applicant to obtain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance. During the exclusivity period, the FDA may not approve or even accept for review an abbreviated new drug application (ANDA), or an NDA submitted under Section 505(b)(2) (505(b)(2) NDA), submitted by another company for another drug based on the same active moiety, regardless of whether the drug is intended for the same indication as the original innovative drug or for another indication, where the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement to one of the patents listed with the FDA by the innovator NDA holder.

The FDCA alternatively provides three years of marketing exclusivity for an NDA, or supplement to an existing NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the modification for which the drug received approval on the basis of the new clinical investigations and does not prohibit the FDA from approving ANDAs or 505(b)(2) NDAs for drugs containing the active agent for the original indication or condition of use. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA. However, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to any preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

Pediatric exclusivity is another type of marketing exclusivity available in the United States. Pediatric exclusivity provides for an additional six months of marketing exclusivity attached to another period of exclusivity if a sponsor conducts clinical trials in children in response to a written request from the FDA. The issuance of a written request does not require the sponsor to undertake the described clinical trials. In addition, orphan drug exclusivity, as described above, may offer a seven-year period of marketing exclusivity, except in certain circumstances.

FDA Approval and Regulation of Companion Diagnostics

If safe and effective use of a therapeutic product depends on an *in vitro* diagnostic medical device, then the FDA generally will require approval or clearance of that diagnostic, known as an *in vitro* companion diagnostic device, at the same time that the FDA approves the therapeutic product. In August 2014, the FDA issued final guidance clarifying the requirements that will apply to approval of therapeutic products and *in vitro* companion diagnostic devices. According to the guidance, for novel drugs, an *in vitro* companion diagnostic device and its corresponding therapeutic should be approved or cleared contemporaneously by the FDA for the use indicated in the therapeutic product's labeling.

If the FDA determines that an *in vitro* companion diagnostic device is essential to the safe and effective use of a novel therapeutic product or indication, the FDA generally will not approve the therapeutic product or new therapeutic product indication if the *in vitro* companion diagnostic device is not approved or cleared for that indication. Approval or clearance of the *in vitro* companion diagnostic device will ensure that the device has been adequately evaluated and has adequate performance characteristics in the intended population.

Under the FDCA, *in vitro* diagnostics, including *in vitro* companion diagnostic devices, are generally regulated as medical devices. In the United States, the FDCA and its implementing regulations, and other federal and state statutes and regulations govern, among other things, medical device design and development, preclinical and clinical testing, premarket clearance or approval, registration and listing, manufacturing, labeling, storage, advertising and promotion, sales and distribution, export and import, and post-market surveillance. Unless an exemption applies, diagnostic tests require marketing clearance or approval from the FDA prior to commercial distribution. The two primary types of FDA marketing authorization applicable to a medical device are premarket notification, also called 510(k) clearance, and premarket approval, or PMA approval. The FDA has stated that it generally requires *in vitro* companion diagnostic devices intended to select the patients who will respond to a drug to obtain a PMA for that diagnostic simultaneously with approval of the drug.

The PMA process, including the gathering of clinical and preclinical data and the submission to and review by the FDA, can take several years or longer. It involves a rigorous premarket review during which the applicant must prepare and provide the FDA with reasonable assurance of the device's safety and effectiveness and information about the device and its components regarding, among other things, device design, manufacturing and labeling. In addition, PMAs for certain devices must generally include the results from extensive preclinical and adequate and well-controlled clinical trials to establish the safety and effectiveness of the device for each indication for which FDA approval is sought. In particular, for a diagnostic, a PMA application typically requires data regarding analytical and clinical validation studies. As part of the PMA review, the FDA will typically inspect the manufacturer's facilities for compliance with the Quality System Regulation, or QSR, which imposes elaborate testing, control, documentation and other quality assurance requirements.

PMA approval is not guaranteed, and the FDA may ultimately respond to a PMA submission with a not approvable determination based on deficiencies in the application and require additional clinical trial or other data that may be expensive and time-consuming to generate and that can substantially delay approval. If the FDA's evaluation of the PMA application is favorable, the FDA typically issues an approvable letter requiring the applicant's agreement to specific conditions, such as changes in labeling, or specific additional information, such as submission of final labeling, in order to secure final approval of the PMA. If the FDA's evaluation of the PMA or manufacturing facilities is not favorable, the FDA will deny approval of the PMA or issue a not approvable letter. A not approvable letter will outline the deficiencies in the application and, where practical, will identify what is necessary to make the PMA approvable. The FDA may also determine that additional clinical trials are necessary, in which case the PMA approval may be delayed for several months or years while the trials are conducted and then the data submitted in an amendment to the PMA. If the FDA concludes that the applicable criteria have been met, the FDA will issue a PMA for the approved indications, which can be more

limited than those originally sought by the applicant. The PMA can include post-approval conditions that the FDA believes necessary to ensure the safety and effectiveness of the device, including, among other things, restrictions on labeling, promotion, sale and distribution. Once granted, PMA approval may be withdrawn by the FDA if compliance with post approval requirements, conditions of approval or other regulatory standards are not maintained or problems are identified following initial marketing.

After a device is placed on the market, it remains subject to significant regulatory requirements. Medical devices may be marketed only for the uses and indications for which they are cleared or approved. Device manufacturers must also establish registration and device listings with the FDA. A medical device manufacturer's manufacturing processes and those of its suppliers are required to comply with the applicable portions of the QSR, which cover the methods and documentation of the design, testing, production, processes, controls, quality assurance, labeling, packaging and shipping of medical devices. Domestic facility records and manufacturing processes are subject to periodic unscheduled inspections by the FDA. The FDA also may inspect foreign facilities that export products to the United States.

Regulation of Combination Products in the United States

Certain product are comprised of components, such as drug components and device components, that would normally be subject to different regulatory frameworks by the FDA and frequently regulated by different centers at the FDA. These products are known as combination products. Under the FDCA, the FDA is charged with assigning a center with primary jurisdiction, or a lead center, for review of a combination product. The determination of which center will be the lead center is based on the "primary mode of action" of the combination product. Thus, if the primary mode of action of a drug-device combination product is attributable to the drug product, the FDA center responsible for premarket review of the drug product would have primary jurisdiction for the combination product. The FDA has also established the Office of Combination Products to address issues surrounding combination products and provide more certainty to the regulatory review process. That office serves as a focal point for combination product issues for agency reviewers and industry. It is also responsible for developing guidance and regulations to clarify the regulation of combination products, and for assignment of the FDA center that has primary jurisdiction for review of combination products where the jurisdiction is unclear or in dispute. A combination product with a primary mode of action attributable to the drug component generally would be reviewed and approved pursuant to the drug approval processes set forth in the FDCA. In reviewing the NDA for such a product, however, FDA reviewers would consult with their counterparts in the device center to ensure that the device component of the combination product met applicable requirements regarding safety, effectiveness, durability and performance. In addition, under FDA regulations, combination products are subject to cGMP requirements applicable to both drugs and devices, including the QSR applicable to medical devices.

Regulation and Procedures Governing Approval of Medicinal Products in the European Union

In addition to regulations in the United States, we will be subject to a variety of foreign regulations governing clinical trials and commercial sales and distribution of setmelanotide to the extent we choose to sell any setmelanotide outside of the United States. Whether or not we obtain FDA approval for a product, we must obtain approval of a product by equivalent competent authorities in foreign jurisdictions before we can commence clinical trials or marketing of the product in those countries. The approval process varies from country to country and the time may be longer or shorter than that required for FDA approval. The requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from country to country. As in the United States, post-approval regulatory requirements, such as those regarding product manufacture, marketing, pharmacovigilance, promotion, advertising or distribution would apply to any product that is approved outside the United States.

The process governing the marketing authorization of medicinal products in the European Union entails satisfactory completion of preclinical studies and adequate and well-controlled clinical trials to establish the safety, quality and efficacy of the medicinal product for each proposed therapeutic indication. It also requires the submission to the relevant competent authorities of a marketing authorization application, or MAA, and granting of a marketing authorization by these authorities before the product can be marketed and sold in the European Union.

Clinical Trial Approval

The Clinical Trials Directive 2001/20/EC, the Directive 2005/28/EC on Good Clinical Practice, or GCP, and the related national implementing provisions of the individual EU member states govern the system for the approval of conduct of clinical trials in the European Union. Under this system, an applicant must obtain prior approval from the competent national authority of the EU member states in which the clinical trial is to be conducted. Furthermore, the applicant may only start a clinical trial at a specific study site after the competent ethics committee has issued a favorable opinion. The clinical trial application must be accompanied by, among other documents, an investigational medicinal product dossier (the Common Technical Document) with supporting information prescribed by Directive 2001/20/EC, Directive 2005/28/EC, where relevant the implementing national provisions of the individual EU member states and further detailed in applicable guidance documents.

In April 2014, the new Clinical Trials Regulation, (EU) No 536/2014 (Clinical Trials Regulation) was adopted. The Regulation is expected to enter into force by the end of 2021, but this could be delayed. The Clinical Trials Regulation will be directly applicable in all the EU member states, repealing the current Clinical Trials Directive 2001/20/EC. Conduct of all clinical trials performed in the European Union will continue to be bound by currently applicable provisions until the new Clinical Trials Regulation becomes applicable. The extent to which on-going clinical trials will be governed by the Clinical Trials Regulation will depend on when the Clinical Trials Regulation becomes applicable and on the duration of the individual clinical trial. If a clinical trial continues for more than three years from the day on which the Clinical Trials Regulation becomes applicable the Clinical Trials Regulation will at that time begin to apply to the clinical trial.

The new Clinical Trials Regulation aims to simplify and streamline the approval of clinical trials in the European Union. The Clinical Trials Regulation introduces a complete overhaul of the existing legislation governing clinical trials for medicinal products in the EU. This includes a new coordinated procedure for authorization of clinical trials that is reminiscent of the mutual recognition procedure for marketing authorization of medicinal products, and increased obligations on sponsors to publish clinical trial results. The main characteristics of the regulation include: a streamlined application procedure via a single entry point, the "EU portal"; a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures for clinical trial sponsors; and a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts. Part I is assessed by the competent authorities of all EU member states in which an application for authorization of a clinical trial has been submitted (member states concerned). Part II is assessed separately by each member state concerned. Strict deadlines have been established for the assessment of clinical trial applications. The role of the relevant ethics committees in the assessment procedure will continue to be governed by the national law of the concerned EU member state. However, overall related timelines will be defined by the Clinical Trials Regulation.

Marketing Authorization

To obtain a marketing authorization for a product under European Union regulatory systems, an applicant must submit an MAA either under a centralized procedure administered by the European Medicines Agency, or EMA, or one of the procedures administered by competent authorities in the EU member states (decentralized procedure, national procedure or mutual recognition procedure). A marketing authorization may be granted only to an applicant established in the European Union. Regulation (EC) No 1901/2006 provides that prior to obtaining a marketing authorization in the European Union, applicants have to demonstrate compliance with all measures included in an EMA-approved Pediatric Investigation Plan, or PIP, covering all subsets of the pediatric population, unless the EMA has granted (1) a product-specific waiver, (2) a class waiver or (3) a deferral for one or more of the measures included in the PIP. By a decision of 15 June 2018, the EMA formally accepted the PIPs for setmelanotide in the treatment of appetite and general nutritional disorders. This included the deferral and waiver requested by us.

The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid for all EEA member states (i.e., the member states of the EU in addition to Iceland, Liechtenstein and Norway). Pursuant to Regulation (EC) No 726/2004, the centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy products and products with a new active substance indicated for the treatment of certain diseases, including products for the treatment of cancer. Medicinal products that contain a new active substance that is not yet authorized in

the EEA and medicinal products that constitute a significant therapeutic, scientific or technical innovation or for which a centralized process is in the interest of patients within the EU fall within the optional scope of the centralized marketing authorization procedure.

Under the centralized procedure, the EMA's Committee for Human Medicinal Products, or the CHMP, is responsible for conducting the initial assessment of a product. The CHMP is also responsible for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of an MAA by the CHMP is 210 days, excluding clock stops, when additional information or written or oral explanation is to be provided by the applicant in response to questions of the CHMP. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation. If the CHMP accepts such request, the time limit of 210 days will be reduced to 150 days but it is possible that the CHMP can revert to the standard time limit for the centralized procedure if it considers that it is no longer appropriate to conduct an accelerated assessment. At the end of this period, the EMA's CHMP provides a scientific opinion on whether or not a marketing authorization should be granted in relation to a medicinal product. Within 15 calendar days of receipt of a final opinion from the CHMP, the European Commission must prepare a draft decision concerning an application for marketing authorization. This draft decision must take the opinion and any relevant provisions of EU law into account. Before arriving at a final decision on an application for centralized authorization of a medicinal product the European Commission must consult the Standing Committee on Medicinal Products for Human Use. The Standing Committee is composed of representatives of the EU member states and chaired by a non-voting European Commission representative. The European Parliament also has a related "droit de regard". The European Parliament's role is to ensure that the European Commission has not exceeded its powers in deciding to grant or refuse to grant a marketing authorization.

The EMA offers the possibility to medicinal product developers to participate in a voluntary scheme of enhanced interaction and early dialogue with the EMA, to enhance support for the development of medicinal products that target an unmet medical need. This voluntary scheme is called PRIority MEdicine support scheme, or PRIME. The PRIME scheme focuses on medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options. These medicines are considered priority medicines by the EMA. To be accepted for PRIME, a medicine has to show its potential to benefit patients with unmet medical needs based on early clinical data. The benefits of a PRIME designation include the appointment of an EMA Committee for Medicinal Products for Human Use rapporteur before submission of the marketing authorization application, early dialogue and scientific advice at key development milestones, and the potential to qualify products for accelerated review earlier in the application process. PRIME designation do not however change the standards for product approval, and there is no assurance that any such designation or eligibility will result in expedited review or approval.

Unlike the centralized authorization procedure, the decentralized marketing authorization procedure requires a submission of a separate application to, and leads to grant of separate marketing authorizations by, the competent authorities of each EU member state in which the product is to be marketed. This application is identical to the application that would be submitted to the EMA for authorization through the centralized procedure. The assessment of the application for marketing authorization is conducted by the reference EU member state. This reference EU member state prepares a draft assessment and drafts of the related materials within 120 days after receipt of a valid application. The resulting assessment report is submitted to the concerned EU member states who, within 90 days of receipt, must decide whether to approve the assessment report and related materials. If a concerned EU member state cannot approve the assessment report and related materials due to concerns relating to a potential serious risk to public health, disputed elements may be referred to the Heads of Medicines Agencies, or CMDh for review. This review, which may also be escalated to the CHMP in case of disagreement in CMDh would result in a decision by the European Commission, whose decision is binding on all EU member states.

The mutual recognition procedure permits companies that have a medicinal product already authorized in one EU member state to apply for this authorization to be recognized by the competent authorities in other EU member states. The national marketing authorization procedure is founded on the same basic EU regulatory process as the other marketing authorization procedures discussed in this Section. The national marketing authorization procedure, which is increasingly

rare, permits a company to submit an application to the competent authority of a single EU member state and, if successful, to obtain a marketing authorization that is valid only in this EU member state.

Regulatory Data Protection in the European Union

In the European Union, innovative medicinal products authorized on the basis of a complete independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity pursuant to Directive 2001/83/EC. Regulation (EC) No 726/2004 repeats this entitlement for medicinal products authorized in accordance the centralized authorization procedure. Data exclusivity prevents applicants for authorization of generics or biosimilars of these innovative products from referencing the innovator's data to assess a generic (abbreviated) or biosimilar application for a period of eight years. During an additional two-year period of market exclusivity, an application for the marketing authorization of a generic or biosimilar medicinal product can be submitted and a related marketing authorization may be granted, and the innovator's data may be referenced, but no generic or biosimilar medicinal product can be placed on the European Union market until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Even if a medicinal product is granted data and market exclusivity, another company nevertheless could also market another version of the product if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Periods of Authorization and Renewals

A marketing authorization has an initial validity for five years in principle. The marketing authorization may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the EMA or by the competent authority of the EU member state. To this end, the marketing authorization holder must provide the EMA or the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization ceases to be valid. The European Commission or the competent authorities of the EU member states may decide, on justified grounds relating to pharmacovigilance, to proceed with one further five year period of marketing authorization. Once subsequently definitively renewed, the marketing authorization shall be valid for an unlimited period. Any authorization which is not followed by the actual placing of the medicinal product on the European Union market (in case of centralized procedure) or on the market of the authorizing EU member state within three years after authorization ceases to be valid (the so-called sunset clause).

Orphan Drug Designation and Exclusivity

Regulation (EC) No. 141/2000, as implemented by Regulation (EC) No. 847/2000 provides that a medicinal product can be designated as an orphan drug by the European Commission if its sponsor can establish: that the product is intended for the diagnosis, prevention or treatment of (1) a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the European Union when the application is made, or (2) a life-threatening, seriously debilitating or serious and chronic condition in the European Union and that without incentives it is unlikely that the marketing of the medicinal product in the European Union would generate sufficient return to justify the necessary investment. For either of these conditions, the applicant must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the European Union or, if such method exists, the medicinal product will be of significant benefit to those affected by that condition.

Once authorized, orphan medicinal products are entitled to 10 years of market exclusivity in all EU member states and in addition a range of other benefits during the development and regulatory review process including scientific assistance for study protocols, authorization through the centralized marketing authorization procedure covering all EU member states and a reduction or elimination of registration and marketing authorization fees. However, marketing authorization may be granted to a similar medicinal product with the same orphan indication during the 10 year period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted

to a similar medicinal product with the same orphan indication if this product is safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, be reduced to six years if it can be demonstrated on the basis of available evidence that the original orphan medicinal product is sufficiently profitable not to justify maintenance of market exclusivity

Regulatory Requirements after a Marketing Authorization has been Obtained

In case an authorization for a medicinal product in the European Union is obtained, the holder of the marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products. These include:

- Compliance with the European Union's stringent pharmacovigilance or safety reporting rules must be ensured. These rules can impose post-authorization studies and additional monitoring obligations.

- The manufacturing of authorized medicinal products, for which a separate manufacturer's license is mandatory, must also be conducted in strict compliance with the applicable European Union laws, regulations and guidance, including Directive 2001/83/EC, Directive 2003/94/EC, Regulation (EC) No 726/2004 and the European Commission Guidelines for Good Manufacturing Practice. These requirements include compliance with European Union cGMP standards when manufacturing medicinal products and active pharmaceutical ingredients, including the manufacture of active pharmaceutical ingredients outside of the European Union with the intention to import the active pharmaceutical ingredients into the European Union.

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

Regulatory Procedure Governing CE marking Companion Diagnostics in the European Union

In the European Union, *in vitro* medical devices are required to conform with the essential requirements of the European Union Directive on *in vitro* diagnostic medical devices (Directive 98/79/EC, as amended). To demonstrate compliance with the essential requirements, the manufacturer must undergo a conformity assessment procedure. The conformity assessment varies according to the type of *in vitro* diagnostic medical device. The conformity assessment of *in vitro* diagnostic medical devices can require the intervention of a Notified Body, which is an organization designated by the competent authorities of an EU member state to conduct conformity assessments. The Notified Body will issue a CE Certificate of Conformity following successful completion of a conformity assessment procedure conducted in relation to the *in vitro* diagnostic medical device and its manufacturer and their conformity with the requirements of the Directive. This Certificate entitles the manufacturer to affix the CE mark to its medical device after having prepared and signed a related EC Declaration of Conformity. For *in vitro* diagnostic medical devices which do not require the intervention of a notified body, the manufacturer can issue an EC Declaration of Conformity based on a self-assessment of the conformity of its products with the Essential Requirements laid down in the *in vitro* diagnostic medical device Directive.

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

Brexit and the Regulatory Framework in the United Kingdom

Following a national referendum and enactment of legislation by the government of the United Kingdom, the United Kingdom formally withdrew from the EU on January 31, 2020 (commonly referred to as "Brexit") and entered into a transition period which ended on December 31, 2020. Since the expiry of the transition period, the United Kingdom operates under a distinct regulatory regime. EU pharmaceutical laws only apply to the United Kingdom in respect of Northern Ireland (as laid out in the Protocol on Ireland and Northern Ireland). Since January 1, 2021, the EU laws which have been transposed into UK law through secondary legislation continue to be applicable as "retained EU law". As there is no general power to amend these regulations, the UK government has introduced a new Medicines and Medical Devices Bill which seeks to address regulatory gaps through implementing regulations and delegated powers covering the fields of human medicines, clinical trials of human medicines, veterinary medicines and medical devices. The purpose of the bill is to enable the existing UK regulatory frameworks to be updated. Although regulatory authorities in the UK have indicated in the bill that new UK rules will closely align with EU laws, detailed proposals are yet to be published. Significant political and economic uncertainty therefore remains about how much the relationship between the United Kingdom and EU will differ as a result of the United Kingdom's withdrawal.

On December 24, 2020, the United Kingdom and the EU announced that they had agreed to the terms of their future trading relationship in the EU—United Kingdom Trade and Cooperation Agreement, or TCA, which has been provisionally applicable since January 1, 2021, but which awaits the final agreement of the remaining 27 EU member states. While agreement on the terms of the TCA has avoided a " no deal" Brexit scenario, and provides in principle for quota- and tariff-free trading of goods, it is nevertheless expected that the TCA will result in the creation of non-tariff barriers (such as increased shipping and regulatory costs and complexities) to the trade in goods between the United Kingdom and the EU. Further, the TCA does not provide for the continued free movement of services between the United Kingdom and the EU and imposes additional restrictions on the free movement of people between the United Kingdom and the EU. The TCA includes provisions affecting pharmaceutical companies such as customs and tariffs in relation to healthcare products and provides for the mutual recognition of Good Manufacturing Practice (GMP) inspections of manufacturing facilities for medicinal products and GMP documents issued. It is important to note however that significant regulatory gaps still exist and the TCA does not contain wholesale mutual recognition of United Kingdom and EU pharmaceutical regulations and product standards, for example in relation to batch testing and pharmacovigilance, which remain subject to further bilateral discussions..

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

Pharmaceutical Coverage and Reimbursement

In the United States and markets in other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on Government and third-party payors to reimburse all or part of the associated healthcare costs. Patients are unlikely to use IMCIVREE unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our products. Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Sales will depend, in part, on the extent to which third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations, provide coverage, and establish adequate reimbursement levels for, IMCIVREE and other product candidates we may develop and obtain approval for in the future. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged, examining the medical necessity, and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable marketing approvals. Nonetheless, setmelanotide may not be considered medically necessary or cost effective. A decision by a third-party payor not to cover IMCIVREE or any of our product candidates, if approved, could reduce physician utilization of our products and have a material adverse effect on our sales, results of operations and financial condition. Additionally, a payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage and reimbursement for the product, and the level of coverage and reimbursement can differ significantly from payor to payor. Third-party reimbursement and coverage may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

The containment of healthcare costs also has become a priority of federal, state and foreign governments and the prices of products have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit a company's revenue generated from the sale of any approved products. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which a company or its collaborators receive marketing approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Outside the United States, ensuring adequate coverage and payment for setmelanotide will face challenges. Pricing of prescription pharmaceuticals is subject to governmental control in many countries. Pricing negotiations with governmental authorities can extend well beyond the receipt of regulatory marketing approval for a product and may require us to conduct a clinical trial that compares the cost effectiveness of setmelanotide or products to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in our commercialization efforts.

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular medicinal product candidate to currently available therapies or so called Health Technology Assessments, in order to obtain reimbursement or pricing approval. For example, the European Union provides options for its member states to restrict the range of products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. EU member states may approve a specific price for a product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other EU member states allow companies to fix their own prices for products, but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. The downward pressure on healthcare costs in general, and particularly in relation to

prescription only medicinal products, has become more intense. As a result, increasingly high barriers are being erected to the entry of new products.

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

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

Healthcare Laws and Regulations

We are subject to healthcare regulation and enforcement by the federal government and the states where we conduct business. These laws include, without limitation, state and federal anti-kickback, fraud and abuse, false claims, and physician and other healthcare provider payment transparency laws and regulations. Foreign governments also have comparable regulations.

The federal Anti-Kickback Statute prohibits, among other things, any person from knowingly and willfully offering, soliciting, receiving or providing remuneration, directly or indirectly, to induce either the referral of an individual, for an item or service or the purchasing or ordering of a good or service, for which payment may be made under federal healthcare programs such as the Medicare and Medicaid programs. The Anti-Kickback Statute is subject to evolving interpretations. In the past, the government has enforced the Anti-Kickback Statute to reach large settlements with healthcare companies based on sham consulting and other financial arrangements with physicians. Further, a person or entity does not need to have actual knowledge of these statutes or specific intent to violate them to have committed a violation. The majority of states also have anti-kickback laws which establish similar prohibitions and in some cases may apply to items or services reimbursed by any third-party payor, including commercial insurers.

Additionally, the civil False Claims Act prohibits knowingly presenting or causing the presentation of a false, fictitious or fraudulent claim for payment to the U.S. government. Actions under the False Claims Act may be brought by the Attorney General or as a qui tam action by a private individual in the name of the government. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act. Violations of the False Claims Act can result in very significant monetary penalties and treble damages. The federal government is using the False Claims Act, and the accompanying threat of significant liability, in its investigation and prosecution of pharmaceutical and biotechnology companies in connection with the promotion of products for unapproved uses and other sales and marketing

practices. The government has obtained multi-billion dollar settlements under the False Claims Act in addition to individual criminal convictions under applicable criminal statutes. We expect that the government will continue to devote substantial resources to investigating healthcare providers' and manufacturers' compliance with applicable fraud and abuse laws.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created new federal criminal statutes that prohibit, among other things, knowingly and willfully executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of these statutes or specific intent to violate them to have committed a violation.

The federal civil monetary penalties laws, impose civil fines for, among other things, the offering or transfer of remuneration to a Medicare or state healthcare program beneficiary if the person knows or should know it is likely to influence the beneficiary's selection of a particular provider, practitioner, or supplier of services reimbursable by Medicare or a state healthcare program, unless an exception applies.

In addition, there has been increased federal and state regulation of payments made to physicians and other healthcare providers. The Physician Payments Sunshine Act imposes new reporting requirements on drug manufacturers for payments made by them to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), certain health care professionals beginning in 2022 and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Drug manufacturers must report such payments to the government by the 90th day of each calendar year.

State and foreign laws and regulations restrict business practices in the pharmaceutical industry and complicate our compliance efforts. For example, some states require companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the federal government's compliance guidance or otherwise restrict payments to healthcare providers and other potential referral sources. Some states require manufacturers to file reports relating to pricing and marketing information. Some state and local governments require the public registration of pharmaceutical sales representatives. Certain states also mandate implementation of commercial compliance programs, impose restrictions on drug manufacturer marketing practices and/or require the tracking and reporting of gifts, compensation and other remuneration to physicians.

Violation of any of such laws or any other governmental regulations that may apply to drug manufacturers may result in penalties, including, without limitation, civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs and imprisonment.

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

Payments made to physicians in certain EU member states must be publicly disclosed. Moreover, agreements with physicians must often be the subject of prior notification and approval by the physician's employer, their competent professional organization, and/or the competent authorities of the individual EU member states. These requirements are provided in the national laws, industry codes, or professional codes of conduct, applicable in the individual EU member states. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

Failure to comply with the EU member state laws implementing the Community Code on medicinal products, and EU rules governing the promotion of medicinal products, interactions with physicians, misleading and comparative

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

Data Privacy and Security

Numerous federal, state and foreign laws and regulations also govern the privacy and security of health information and the collection, use, disclosure, and protection of health-related and other personal information, including state data breach notification laws, state health information and/or genetic privacy laws, and federal and state consumer protection laws, such as Section 5 of the FTC Act, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts. Compliance with these laws is difficult, constantly evolving, and time consuming, and companies that do not comply with these state laws may face civil penalties.

For example, HIPAA, as amended, regulations implemented thereunder, impose obligations with respect to safeguarding the privacy, security and transmission of individually identifiable health information. We may obtain health information from third parties (including research institutions from which we obtain clinical trial data) that are subject to privacy and security requirements under HIPAA. Although we are not directly subject to HIPAA – other than with respect to providing certain employee benefits – we could potentially be subject to criminal penalties if we, our affiliates, or our agents knowingly obtain, use, or disclose individually identifiable health information maintained by a HIPAA-covered entity in a manner that is not authorized or permitted by HIPAA. Further, in California, the California Consumer Privacy Act, or the CCPA, took effect on January 1, 2020. The CCPA establishes certain requirements for data use and sharing transparency and creates new data privacy rights for consumers. These laws and regulations are evolving and subject to interpretation, and may impose limitations on our activities or otherwise adversely affect our business. Further, the California Privacy Rights Act ("CPRA") was recently voted into law by California residents. The CPRA significantly amends the CCPA, and imposes additional data protection obligations on covered companies doing business in California, including additional consumer rights processes and opt outs for certain uses of sensitive data. It also creates a new California data protection agency specifically tasked to enforce the law, which would likely result in increased regulatory scrutiny of California businesses in the areas of data protection and security. The substantive requirements for businesses subject to the CPRA will go into effect on January 1, 2023, and become enforceable on July 1, 2023. Similarly, there are a number of legislative proposals in the European Union, the United States, at both the federal and state level, as well as other jurisdictions that could impose new obligations or limitations in areas affecting our business. In addition, some countries are considering or have passed legislation implementing data protection requirements or requiring local storage and processing of data or similar requirements that could increase the cost and complexity of delivering our services and research activities. These laws and regulations, as well as any associated claims, inquiries or investigations or any other government actions may lead to unfavorable outcomes including increased compliance costs, delays or impediments in the development of new products, negative publicity, increased operating costs, diversion of management time and attention, and remedies that harm our business, including fines or demands or orders that we modify or cease existing business practices.

The EU, United Kingdom, Switzerland and other countries have also adopted data protection laws and regulations, which impose significant compliance obligations. In the EU, the collection and use of personal health data is governed by the provisions of the General Data Protection Regulation, or GDPR. The GDPR became effective on May 25, 2018, repealing the Data Protection Directive and increasing our responsibility and liability in relation to the processing of personal data of EU subjects. Fines for certain breaches of the GDPR are significant, up to the greater of 20 million Euros or 4 % of total global annual turnover. In addition to the foregoing, a breach of the GDPR could result in regulatory investigations, reputational damage, orders to cease/change our processing of our data, enforcement notices, and/or assessment notices (for a compulsory audit). We may also face civil claims including representative actions and other class action type litigation (where individuals have suffered harm), potentially amounting to significant compensation or damages liabilities, as well as associated costs, diversion of internal resources, and reputational harm. Additionally, from 1 January 2021, we are subject to the GDPR and also the United Kingdom GDPR, which, together with the amended United Kingdom Data Protection Act 2018, retains the GDPR in United Kingdom national law following Brexit. The United Kingdom GDPR mirrors the fines under the GDPR, e.g. fines up to the greater of €20 million (£17.5 million) or

4% of global turnover. The relationship between the United Kingdom and the European Union in relation to certain aspects of data protection law remains unclear, and it is unclear how United Kingdom data protection laws and regulations will develop in the medium to longer term. These changes will lead to additional costs and increase our overall risk exposure.

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

With respect to the transfer of personal data out of the EU and the United Kingdom, the GDPR and the United Kingdom provides that the transfer of personal data to countries that are not considered by the European Commission to provide an adequate level of data protection, including the United States, is permitted only on the basis of complying with specific legal steps, a number of which are subject to legal challenges. Most recently, on July 16, 2020, the Court of Justice of the European Union ("CJEU") invalidated the EU-US Privacy Shield Framework ("Privacy Shield") under which personal data could be transferred from the EEA to US entities who had self-certified under the Privacy Shield scheme. These recent developments may require us to review and amend the legal mechanisms by which we make and/ or receive personal data transfers to/ in the U.S. As supervisory authorities issue further guidance on personal data export mechanisms, including circumstances where the standard contractual clauses cannot be used, and/or start taking enforcement action, we could suffer additional costs, complaints and/or regulatory investigations or fines, and/or if we are otherwise unable to transfer personal data between and among countries and regions in which we operate, it could affect the manner in which we provide our services, the geographical location or segregation of our relevant systems and operations, and could adversely affect our financial results. In addition, the United Kingdom's withdrawal from the European Union means that the United Kingdom will become a "third country" for the purposes of data transfers from the European Union to the United Kingdom following the expiration of the four to six-month personal data transfer grace period (from 1 January 2021) set out in the EU and United Kingdom Trade and Cooperation Agreement, unless a relevant adequacy decision is adopted in favor of the United Kingdom (which would allow data transfers without additional measures). These changes may require us to find alternative solutions for the compliant transfer of personal data into the United Kingdom.

Healthcare Reform

A primary trend in the United States healthcare industry and elsewhere is cost containment. There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biopharmaceutical products, limiting coverage and reimbursement for drugs and other medical products, government control and other changes to the healthcare system in the United States.

By way of example, the United States and state governments continue to propose and pass legislation designed to reduce the cost of healthcare. In March 2010, the Patient Protection and Affordable Care Act, or signed the ACA, was signed into law, which, among other things, included changes to the coverage and payment for products under government health care programs. Among the provisions of the ACA of importance to IMCIVREE and our potential drug candidates are:

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

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

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

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

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

- established the Medicare Part D coverage gap discount program by requiring manufacturers to provide a 70% point-of-sale-discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D;

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

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

Since its enactment, there have been judicial, executive and Congressional challenges to certain aspects of the ACA. For example, the Tax Cuts and Jobs Acts (the "Tax Act") was enacted, which, among other things, removed penalties for not complying with the individual mandate to carry health insurance. On December 14, 2018, a U.S. District Court Judge in the Northern District of Texas, ruled that the individual mandate is a critical and inseverable feature of the ACA, and therefore, because it was repealed as part of the Tax Act, the remaining provisions of the ACA are invalid as well. On December 18, 2019, the U.S. Court of Appeals for the 5th Circuit upheld the District Court's decision that the individual mandate was unconstitutional but remanded the case back to the District Court to determine whether the remaining provisions of the Affordable Care Act are invalid as well. The U.S. Supreme Court is currently reviewing the case, although it is unclear how the Supreme Court will rule. In addition, there may be other efforts to challenge, replace or repeal the ACA that may affect the law or our business.

Other legislative and regulatory changes have been proposed and adopted in the United States since the ACA was enacted. These changes included an aggregate reduction in Medicare payments to providers of 2 percent per fiscal year, which went into effect on April 1, 2013 and will remain in effect through 2030, with the exception of a temporary suspension from May 1, 2020 through March 31, 2021, unless additional Congressional action is taken. In addition, the American Taxpayer Relief Act of 2012, which further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Moreover, the federal government and individual states in the United States have become increasingly active in developing proposals, passing legislation and implementing regulations designed to control drug pricing, including price or patient reimbursement constraints, discounts, formulary flexibility, marketing cost disclosure and transparency measures. These new laws and the regulations and policies implementing them, as well as other healthcare-related measures that may be adopted in the future, could materially reduce our ability to develop and commercialize IMCIVREE™ and our product candidates, if approved.

Human Capital

Our employees are dedicated to our mission of changing the paradigm for the treatment of rare genetic diseases of obesity. As of January 31, 2021, we had approximately 90 employees, most of whom were located at our corporate headquarters in Boston with approximately 15 employees located in various regions in the United States as well as Europe, as we start to build out a broader national and global presence. We also work with consultants and contractors to provide both specific expertise and flexibility for our business needs.

We believe that our future success largely depends upon our continued ability to attract and retain highly skilled employees. We emphasize a number of measures and objectives in managing our human capital assets, including, among others, employee engagement, development and training, talent acquisition and retention, employee wellness, diversity, inclusion, and compensation and pay equity. We provide our employees with competitive salaries, bonuses, opportunities for equity ownership, development opportunities that enable continued learning and growth and a robust employment package that promotes well-being across all aspects of their lives, including health care, retirement planning and paid time off. In addition, we regularly collect employee feedback to ensure two-way communication, measure employee engagement and identify opportunities for improvement. During 2020, in response to the COVID-19 pandemic and its impact on the workplace, we executed what we believe was a smooth transition to a remote work environment while ensuring that ample resources, support and flexibility were available to our employees.

We believe that developing a diverse and inclusive culture is critical to continuing to attract and retain the top talent necessary to deliver on our growth strategy. As such, we are investing in a work environment where our employees feel inspired and included. We continue to focus on extending our diversity and inclusion initiatives across our entire workforce. In addition, we work to ensure our employees understand and embrace our commitment to our patient community and our focus on changing the paradigm for treatment of rare genetic diseases of obesity. We value our employees' courage to ask bold questions and their commitment to learning and collaboration, as each person brings a unique contribution to furthering our mission. Grounded in these guiding principles, we believe we have developed a collaborative environment where our colleagues feel respected, valued, and can contribute to their fullest potential.

Corporate Information

We are a Delaware corporation organized in February 2013. We were originally incorporated 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 website is www.rhythmtx.com. Information that is contained on, or that can be accessed through, our website is not incorporated by reference into this Annual Report on Form 10-K, and you should not consider information on our website to be part of this Annual Report on Form 10-K.

Available Information

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

Item 1A. Risk Factors

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

Risks Related to Our Financial Position and Need for Capital

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

We are a commercial-stage biopharmaceutical company with a limited operating history on which to base your investment decision. Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. We were incorporated in February 2013. Our operations to date have been limited primarily to acquiring rights to intellectual property, business planning, raising capital, developing our technology, identifying potential product candidates, undertaking preclinical studies and conducting research and development activities, including clinical trials, for setmelanotide. We have never generated any revenue from product sales. We have obtained FDA approval for IMCIVREE™ (setmelanotide) for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to proopiomelanocortin, or POMC, proprotein convertase subtilisin/kexin type 1, or PCSK1, or leptin receptor, or LEPR, deficiency confirmed by genetic testing, but we have not obtained any other regulatory approvals for setmelanotide. We first commercialized IMCIVREE in the U.S. in the first quarter of 2021and therefore do not have a long history operating as a commercial company. We will need to begin transitioning from a company with a research and development focus to a company capable of supporting commercial activities and we may not be successful in such a transition. We have not yet demonstrated our ability to manufacture at commercial scale, or arrange for a third party to do so on our behalf, or conduct sales, marketing and distribution activities necessary for successful product commercialization. Consequently, any predictions made about our future success or viability may not be as accurate as they could be if we had a longer operating history.

Since our inception, we have focused substantially all of our efforts and financial resources on the research and development of setmelanotide, which is FDA approved as noted above and currently in clinical development for Bardet-Biedl syndrome, or BBS, Alström syndrome, and other indications. We have funded our operations to date primarily through the proceeds from the sales of common stock and preferred stock, asset sales, as well as capital contributions from our former parent, Rhythm Holdings LLC, and have incurred losses in each year since our inception.

Our net losses were $134.0 million and $140.7 million for the years ended December 31, 2020 and 2019, respectively. As of December 31, 2020, we had an accumulated deficit of $459.3 million. Substantially all of our operating losses have resulted from costs incurred in connection with our development programs and from commercial and general and administrative costs associated with our operations. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our stockholders' deficit and working capital. We expect our research and development expenses to significantly increase in connection with our additional clinical trials of setmelanotide and development of any other product candidates we may choose to pursue. In addition, having obtained marketing approval for IMCIVREE, we will incur significant sales, marketing and outsourced manufacturing expenses. We will incur additional costs associated with operating as a public company, including as a result of no longer qualifying as an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. As a result, we expect to continue to incur significant and increasing operating losses for the foreseeable future. Because of the numerous risks and uncertainties associated with developing pharmaceutical products, we are unable to predict the extent of any future losses or when we will become profitable, if at all. Even if we do become profitable, we may not be able to sustain or increase our profitability on a quarterly or annual basis.

Our ability to become profitable depends upon our ability to generate revenue. To date, we have not generated any revenue from setmelanotide, and we do not know when, or if, we will generate any revenue. Our ability to generate revenue depends on a number of factors, including, but not limited to, our ability to:

- commercialize setmelanotide by building a commercial organization and/or entering into collaborations with third parties; and
- ensure setmelanotide is available to patients;
- achieve market acceptance of setmelanotide in the medical community and with third-party payors.
- continue to initiate and successfully complete later-stage clinical trials that meet their clinical endpoints;
- continue to initiate and successfully complete all safety studies required to obtain U.S. and foreign marketing approvals for setmelanotide as a treatment for obesity caused by genetic deficiencies affecting the MC4R pathway; and
- successfully manufacture or contract with others to manufacture setmelanotide.

Absent our entering into collaboration or partnership agreements, we expect to incur significant sales and marketing costs as we prepare to commercialize setmelanotide. Even though IMCIVREE is FDA approved for chronic weight management in patients 6 years of age and older with obesity due to POMC, PCSK1 or LEPR deficiencies, and even if we successfully complete our pivotal and other clinical trials and setmelanotide is approved for commercial sale in additional indications, setmelanotide may not be a commercially successful drug. We may not achieve profitability soon after generating product sales, if ever. If we are unable to generate product revenue, we will not become profitable and will be unable to continue operations without continued funding.

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

We are currently in the early stages of commercializing IMCIVREE for chronic weight management in patients with obesity due to POMC, PCSK1 or LEPR deficiencies in the U.S. and advancing setmelanotide through clinical development for additional indications in the United States and for potential approvals in other countries. Developing peptide therapeutic products is expensive and we expect our research and development expenses to increase substantially in connection with our ongoing activities, particularly as we advance setmelanotide in additional clinical trials. We intend to use our available cash resources to advance the clinical development of setmelanotide, for disease-education and community-building activities, precommercialization activities for setmelanotide in BBS, patient identification, and commercialization activities related to IMCIVREE. Depending on the status of additional regulatory approvals and commercialization of setmelanotide, as well as the progress we make in any sales of IMCIVREE, we may still require significant additional capital to fund the continued development of setmelanotide and our operating needs thereafter. We may also need to raise additional funds if we choose to pursue additional indications and/or geographies for setmelanotide or otherwise expand more rapidly than we presently anticipate.

From August 2015 through August 2017, we raised aggregate net proceeds of $80.8 million through our issuance of series A preferred stock. In connection with our initial public offering, or IPO, in October 2017 and our underwritten follow-on offerings through February 2021, we raised aggregate net proceeds of approximately $611.4 million through the issuance of our common stock after deducting underwriting discounts, commissions and offering related transaction costs. Since inception, we have received a further $100.0 million from asset sales, specifically in connection with the sale of our Rare Pediatric Disease Priority Review Voucher, or PRV, to Alexion Pharmaceuticals, Inc. As of December 31, 2020, our cash and cash equivalents and short-term investments were approximately $172.8 million. We expect our cash and cash equivalents and short-term investments as of December 31, 2020, together with the aggregate net proceeds from the February 2021 public offering and proceeds from the PRV Transfer of approximately $260.1 million, will enable us to

fund our operating expenses through at least the second half of 2023. However, our operating plan may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through public or private equity or debt financings, government or other third-party funding, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements, or a combination of these approaches. We will also require additional capital to obtain additional regulatory approvals for, and to continue to commercialize, setmelanotide. Raising funds in the current economic environment, particularly in light of ongoing uncertainty related to the COVID-19 pandemic, may present additional challenges. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or if we have specific strategic considerations.

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

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

Risks Related to the Development of Setmelanotide

The European Medicines Agency, or EMA, may disagree with our interpretation of clinical results obtained from our Phase 3 clinical trials for obesity due to POMC, PCSK1 or LEPR deficiencies, our results do not guarantee that the Marketing Authorization Application, or MAA, will support regulatory approval, and, even if our Phase 3 data are deemed to be positive by the EMA, the EMA may disagree with other aspects of the MAA submission and, as a result, the European Commission may decline to approve setmelanotide for the proposed indications.

Even though the FDA has approved IMCIVREE for chronic weight management in patients with obesity due to POMC, PCSK1 or LEPR deficiencies, the EMA could determine that the data from our Phase 3 clinical trials were negative or inconclusive, not sufficiently meaningful from a clinical perspective or could reach different conclusions than we and the FDA have on the same data. Negative or inconclusive results of a clinical trial or a difference of opinion could cause the European Commission to decline to approve our application or cause the EMA to require us to repeat the trial or conduct additional clinical trials prior to obtaining approval for commercialization, and there is no guarantee that additional trials would achieve positive results to the satisfaction of the EMA or that the EMA will agree with our interpretation of the results. Any such determination by the EMA would delay the timing of our commercialization plan for setmelanotide in Europe or prevent its further development, and adversely affect our business operations. Additionally, the EMA may provide commentary at any time during the review process which could require us to submit additional information and delay the review timeline, adversely affect the review process, or even prevent the approval of setmelanotide, any of which would adversely affect our business. We may not be able to appropriately remedy issues that the EMA may raise in its review of our MAA submission, and we may not have sufficient time or financial resources to conduct future activities to remediate issues raised by the EMA.

There is no guarantee that the data obtained from our Phase 3 clinical trials for obesity due to POMC, PCSK1 or LEPR deficiencies will be supportive of, or guarantee, a successful MAA submission, or result in our obtaining the European Commission’s approval of setmelanotide in a timely fashion and for a commercially viable indication, or at all.

Moreover, even if we obtain approval of setmelanotide in Europe, any such approval might significantly limit the approved indications for use, including by limiting the approved label for use by more limited patient populations than we propose, require that precautions, contraindications or warnings be included on the product labeling, including black box warnings, require expensive and time-consuming post-approval clinical studies, risk evaluation and mitigation strategies, or REMS, or surveillance as conditions of approval, or, through the product label, the approval may limit the claims that we may make, which may impede the successful commercialization of setmelanotide.

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

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

Positive results for one indication are not necessarily predictive of positive results for other indications. We have demonstrated statistically significant and clinically meaningful reductions in weight and hunger in Phase 3 clinical trials in obesity due to POMC, PCSK1 or LEPR deficiencies and BBS, and believe we have demonstrated proof of concept in Phase 2 clinical trials in deficiencies due to a variant in one of the two alleles in the *POMC, PCSK1, or LEPR* genes (HET obesity), as well as the SRC1 and SH2B1 genes, all genetic disorders of extreme and unrelenting appetite and obesity. We hypothesize that patients with other upstream genetic defects in the MC4R pathway may also respond with reductions in weight and hunger after treatment with setmelanotide. However patients with other upstream genetic defects may not have a similar response to setmelanotide, and until we obtain more clinical data in other genetic defects, we will not be sure that we can achieve proof of concept in such indications.

We are actively working to advance additional genetic deficiencies related to the MC4R pathway through our clinical development program. We anticipate initiating a Phase 3, registration-enabling study to evaluate setmelanotide in patients with MC4R pathway deficiencies due to a variant in one of the two alleles in the *POMC, PCSK1, or LEPR* genes (HET obesity), as well as the SRC1 and SH2B1 genes. In addition, we plan to initiate an expanded Phase 2 Basket Study to evaluate setmelanotide for the treatment of obesity due to a deficiency in one of 31 additional genes associated with the MC4R pathway. However, success in a basket trial, or any trial in one indication, may not predict success in another indication. In contrast, in the event of an adverse safety issue, clinical hold, or other adverse finding in one or more indications being tested, such event could adversely affect our trials in the other indications and may delay or prevent completion of the clinical trials.

Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in later stage clinical trials after achieving positive results in early stage development, and we cannot be certain that we will not face similar setbacks. These setbacks have been caused by, among other things, pre-clinical findings made while clinical trials were underway.

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

Interim, "topline" and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.

From time to time, we may publicly disclose preliminary or topline data from our preclinical studies and clinical trials, which is based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular study or trial. For example, the results of our Phase 3 clinical trials for BBS and Alström syndrome that we have publicly disclosed consist of topline data and further analyses of data obtained from these trials. We make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, the topline or preliminary results that we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. Topline data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published or reported. As a result, topline data should be viewed with caution until the final data are available.

From time to time, we may also disclose interim data from our preclinical studies and clinical trials. For example, we recently announced interim proof-of-concept data from our ongoing exploratory Phase 2 Basket Study evaluating setmelanotide in patients with MC4R pathway deficiencies due to a variant in one of the two alleles in the *POMC, PCSK1, or LEPR* genes, as well as the SRC1 and SH2B1 genes. Interim data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. Adverse differences between preliminary or interim data and final data could significantly harm our business prospects. Further, disclosure of interim data by us or by our competitors could result in volatility in the price of our common stock.

Further, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate or product and our company in general. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is based on what is typically extensive information, and you or others may not agree with what we determine is material or otherwise appropriate information to include in our disclosure.

If the interim, topline, or preliminary data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, our product candidates may be harmed, which could harm our business, operating results, prospects or financial condition.

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 500 patients worldwide. This estimate is based on:
    - published prevalence estimates of one in 1,000,000 in North America, which projects to approximately 325 people in the United States. We believe the majority of these patients are addressable patients; and
    - our belief that with wider availability of genetic testing expected for Alström syndrome and increased awareness of new treatments, the number of patients diagnosed with this disorder will increase.
- *POMC, 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 population data and CDC prevalence numbers for early onset obesity (120% the 95th percentile between the ages of 2-5 years);
    - 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-rescuable deficiency obesity is approximately 10,000 patients in the United States. This estimate is based on:
    - U.S. Census Bureau population data and CDC prevalence numbers for early onset obesity (120% the 95th percentile between the ages of 2-5 years);
    - a comprehensive ongoing biochemical screening study indicating there may be a defined subset of individuals who carry MC4R variants that may be rescued by an MC4R agonist; 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 2,400 patients in the United States. This estimate is based on:
    - published prevalence estimates of one in 25,000 in the United States, which projects to approximately 13,000 people in the United States;
    - published prevalence estimates that approximately 10% of patients with Smith-Magenis syndrome have RAI1 variants that may affect the MC4R pathway and 90% of patients with Smith-Magenis syndrome have 17p11.2 chromosomal deletions which also may affect the MC4R pathway, of which approximately 67% and 13%, respectively, live with obesity; and
    - U.S. Census Bureau figures for total population of adults and children.

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

Defining the exact genetic variants that result in MC4R pathway disorders is complex, so if any approval that we obtain is based on a narrower definition of these patient populations than we had anticipated, then the potential market for setmelanotide for these indications will be smaller than we originally believed. In either case, a smaller patient population in our target indications would have a materially adverse effect on our ability to achieve commercialization and generate revenues.

If we experience delays or difficulties in the enrollment and/or retention of patients in clinical trials, our regulatory submissions or receipt of additional marketing approvals could be delayed or prevented.

We may not be able to initiate or continue our planned clinical trials on a timely basis or at all for our product candidates if we are unable to recruit and enroll a sufficient number of eligible patients to participate in these trials through completion of such trials as required by the FDA or other comparable foreign regulatory authorities. Patient enrollment is a significant factor in the timing of clinical trials. Our ability to enroll eligible patients may be limited or may result in slower enrollment than we anticipate.

Our clinical trials will compete with other clinical trials that are in the same therapeutic areas as our product candidates, and this competition reduces the number and types of patients available to us, as some patients who might have opted to enroll in our trials may instead opt to enroll in a trial being conducted by one of our competitors. Because the number of qualified clinical investigators and clinical trial sites is limited, we expect to conduct some of our clinical trials at the same clinical trial sites that some of our competitors use, which will reduce the number of patients who are available for our clinical trials at such clinical trial sites. In addition, there are limited patient pools from which to draw for clinical studies. In addition to the rarity of genetic diseases of obesity, the eligibility criteria of our clinical studies will further limit the pool of available study participants as we will require that patients have specific characteristics that we can measure or to assure their disease is either severe enough or not too advanced to include them in a study. Patient enrollment for our current or any future clinical trials may be affected by other factors, including:

- size and nature of the patient population;
- severity of the disease under investigation;
- availability and efficacy of approved drugs for the disease under investigation;
- patient eligibility criteria for the trial in question as defined in the protocol;
- perceived risks and benefits of the product candidate under study;
- clinicians' and patients' perceptions as to the potential advantages of the product candidate being studied in relation to other available therapies, including any new products that may be approved or future product candidates being investigated for the indications we are investigating;
- clinicians' willingness to screen their patients for genetic markers to indicate which patients may be eligible for enrollment in our clinical trials;
- delays in or temporary suspension of the enrollment of patients in our planned clinical trial due to the COVID-19 pandemic;
- ability to obtain and maintain patient consents;
- patient referral practices of physicians;

- the ability to monitor patients adequately during and after treatment;
- proximity and availability of clinical trial sites for prospective patients; and
- the risk that patients enrolled in clinical trials will drop out of the trials before completion, including as a result of contracting COVID-19 or other health conditions or being forced to quarantine, or, because they may be late-stage cancer patients, will not survive the full terms of the clinical trials.

In addition, the pediatric population is an important patient population for setmelanotide, and our addressable patient population estimates include pediatric populations. However, it may be more challenging to conduct studies in younger subjects, and to locate and enroll pediatric patients. These factors may make it difficult for us to enroll enough patients to complete our clinical trials in a timely and cost-effective manner. Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays or may require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may also result in increased development costs for setmelanotide and any future product candidates and jeopardize our ability to obtain additional marketing approvals for the sale of setmelanotide. Furthermore, even if we are able to enroll a sufficient number of patients for our clinical trials, we may have difficulty maintaining participation in our clinical trials through the treatment and any follow-up periods.

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

Successful completion of our ongoing and planned clinical trials is a prerequisite to submitting an NDA or NDA supplement to the FDA, an MAA to the EMA, and other applications for marketing authorization to equivalent competent authorities in foreign jurisdictions, and consequently, successful completion of such trials will be required for regulatory approvals and the commercial marketing of setmelanotide.

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

- inability to generate sufficient preclinical or other in vivo or *in vitro* data to support the initiation of clinical studies;
- delays in the completion of preclinical laboratory tests, animal studies and formulation studies in accordance with FDA's good laboratory practice requirements and other applicable regulations;
- the FDA or other equivalent competent authorities in foreign jurisdictions may deny permission to proceed with our ongoing or planned trials or any other clinical trials we may initiate, or may place a clinical trial on hold or be suspended;
- delays in filing or receiving authorization to proceed under an additional investigational new drug application, or IND, if required;
- delays in reaching a consensus with the FDA and other regulatory agencies on study design and obtaining regulatory authorization to commence clinical trials;
- delays in reaching or failing to reach agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- difficulties in obtaining Institutional Review Board, or IRB, and/or ethics committee approval to conduct a clinical trial at a prospective site or sites;

- since many already diagnosed patients are at academic sites, delays in conducting clinical trials at academic sites due to the particular challenges and delays typically associated with those sites, as well as the lack of alternatives to these sites which have already-diagnosed patients;
- inadequate quantity or quality of setmelanotide or other materials necessary to conduct clinical trials, including delays in the manufacturing of sufficient supply of finished drug product;
- challenges in identifying, recruiting and training suitable clinical investigators;
- challenges in recruiting and enrolling suitable patients to participate in clinical trials;
- severe or unexpected drug-related side effects experienced by patients in a clinical trial, including side effects previously identified in our completed clinical trials;
- difficulty collaborating with patient groups and investigators;
- failure by our CROs, other third parties or us to perform in accordance with the FDA's or any other regulatory authority's good clinical practice requirements, or GCPs, or applicable regulatory guidelines in other countries;
- occurrence of adverse events associated with setmelanotide that are viewed to outweigh its potential benefits, or occurrence of adverse events in trial of the same or similar class of agents conducted by other companies;
- changes to the clinical trial protocols;
- clinical sites deviating from trial protocol or dropping out of a trial;
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols;
- changes in the standard of care on which a clinical development plan was based, which may require new or additional trials;
- selection of clinical endpoints that require prolonged periods of observation or analyses of resulting data;
- the cost of clinical trials of our product candidates being greater than we anticipate;
- clinical trials of our product candidates producing negative or inconclusive results, which may result in our deciding, or regulators requiring us, to conduct additional clinical trials or abandon development of such product candidates; and
- development of antibodies to the drug or adjuvants may result in loss of efficacy or safety events.

In addition, disruptions caused by the COVID-19 pandemic may increase the likelihood that we encounter such difficulties or delays in initiating, enrolling, conducting or completing our planned and ongoing clinical trials. Clinical trials may also be delayed or terminated as a result of ambiguous or negative interim results. In addition, a clinical trial may be suspended or terminated by us, the FDA or other equivalent competent authorities in foreign jurisdictions, the IRBs or ethics committees at the sites where the IRBs or the ethics committees are overseeing a clinical trial, a data and safety monitoring board, or DSMB, or Safety Monitoring Committee, or SMC, overseeing the clinical trial at issue or other equivalent competent authorities due to a number of factors, including, among others:

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

- inspection of the clinical trial operations or trial sites by the FDA or other equivalent competent authorities that reveals deficiencies or violations that require us to undertake corrective action, including the imposition of a clinical hold;
- unforeseen safety issues, adverse side effects or lack of effectiveness;
- changes in government regulations or administrative actions;
- problems with clinical trial supply materials; and
- lack of adequate funding to continue the clinical trial.

Delays in the completion of any preclinical studies or clinical trials of setmelanotide will increase our costs, slow down our product candidate development and approval process and delay or potentially jeopardize our ability to commence product sales and generate product revenue. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of a regulatory approval for setmelanotide. Any delays to our preclinical studies or clinical trials that occur as a result could shorten any period during which we may have the exclusive right to commercialize setmelanotide and our competitors may be able to bring products to market before we do, and the commercial viability of our product candidates could be significantly reduced. Any of these occurrences may harm our business, financial condition and prospects significantly.

The COVID-19 pandemic has and may continue to adversely impact our business, including our preclinical studies, clinical trials and our commercialization prospects.

The COVID-19 pandemic has spread to multiple countries, including the United States, Canada and Europe, where we have planned or ongoing preclinical studies and clinical trials. Governments from many countries have established stay at home measures including, among other things, the prohibition of public gatherings and restrictions on domestic and international travel. The pandemic and government measures taken in response have also had a significant impact, both direct and indirect, on businesses and commerce, as worker shortages have occurred, supply chains have been disrupted, facilities and production have been suspended, and demand for certain goods and services, such as medical services and supplies, has spiked, while demand for other goods and services, such as travel, has fallen. In response to the spread of COVID-19, we have limited access to our principal executive office with most employees continuing their work outside of our office and restricted travel. In addition, we experienced interruption of key clinical trial activities, such as patient attendance and clinical trial site monitoring, in our Phase 3 clinical trial evaluating setmelanotide for the treatment of insatiable hunger and severe obesity in individuals with BBS or Alström syndrome. If the COVID-19 pandemic continues for a significant length of time, we may experience additional disruptions that could severely impact our business, preclinical studies, clinical trials and our commercialization prospects, including:

- delays in receiving approval from local regulatory authorities to initiate or conduct our planned clinical trials;
- further delays or difficulties in enrolling patients in our clinical trials;
- delays or difficulties in clinical site initiation, including difficulties in recruiting clinical site investigators and clinical site staff;
- delays in clinical sites receiving the supplies and materials needed to conduct our clinical trials, including interruption in global shipping that may affect the transport of clinical trial materials;
- changes in local regulations as part of a response to the COVID-19 pandemic which may require us to change the ways in which our clinical trials are conducted, which may result in unexpected costs, or to discontinue such clinical trials altogether;

- diversion of healthcare resources away from the conduct of clinical trials, including the diversion of hospitals serving as our clinical trial sites and hospital staff supporting the conduct of our clinical trials;

- further interruption of key clinical trial activities, such as clinical trial site monitoring, due to limitations on travel imposed or recommended by federal or state governments, employers and others, or interruption of clinical trial subject visits and study procedures, the occurrence of which could affect the integrity of clinical trial data;

- risk that participants enrolled in our clinical trials will contract COVID-19 while the clinical trial is ongoing, which could impact the results of the clinical trial, including by increasing the number of observed adverse events;

- interruptions or delays in preclinical studies due to restricted or limited operations at our research and development laboratory facility;

- delays in necessary interactions with local regulators, ethics committees and other important agencies and contractors due to limitations in employee resources or forced furlough of government employees;

- limitations in employee resources that would otherwise be focused on the conduct of our clinical trials, including because of sickness of employees or their families or the desire of employees to avoid contact with large groups of people;

- refusal of the FDA to accept data from clinical trials in affected geographies;

- impacts from prolonged remote work arrangements, such as increased cybersecurity risks and strains on our business continuity plans; and

- delays in the receipt of marketing authorizations for our product candidates, which could materially affect our commercialization plans.

The COVID-19 pandemic continues to rapidly evolve. The extent to which the pandemic impacts our business, preclinical studies, clinical trials and our commercialization prospects will depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as the ultimate geographic spread of the disease, the duration of the pandemic, travel restrictions and social distancing in the United States and other countries, business closures or business disruptions, the effectiveness of vaccines and vaccine distribution efforts, and the effectiveness of other actions taken in the United States and other countries to contain and treat the disease. While the potential economic impact brought by and the duration of the COVID-19 pandemic may be difficult to assess or predict, the widespread pandemic has resulted in, and may continue to result in, significant disruption of global financial markets, reducing our ability to access capital, which could in the future negatively affect our liquidity. In addition, the recession or economic downturn resulting from the spread of COVID-19 could materially affect our business.

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

First generation MC4R agonists were predominantly small molecules that failed in clinical trials due to significant safety issues, particularly increases in blood pressure, and had limited efficacy. Undesirable side effects caused by setmelanotide could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive labeling or the delay or denial of additional regulatory approvals by the FDA or other equivalent competent authorities in foreign jurisdictions. Treatment-related side effects could also affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims. Any of these occurrences may prevent us from achieving or maintaining market acceptance of the affected product candidate and may adversely affect our business, financial condition and prospects significantly.

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

- adverse effects on cardiovascular parameters, such as increases in heart rate and blood pressure;
- erections in males and similar effects in women, such as sexual arousal, clitoral swelling and hypersensitivity;
- nausea and vomiting;
- reduced appetite;
- headache;
- effects on mood, depression, anxiety and other psychiatric manifestations; and
- other effects, for which most investigators reported as unrelated to setmelanotide and for which no increased incidence or pattern is currently evident.

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

If these or other significant adverse events or other side effects are observed in any of our ongoing or planned clinical trials, we may have difficulty recruiting patients to the clinical trials, patients may drop out of our trials, or we may be required to abandon the trials or our development efforts of that product candidate altogether. We, the FDA, other comparable regulatory authorities or an IRB may also suspend clinical trials of a product candidate at any time for various reasons, including a belief that subjects in such trials are being exposed to unacceptable health risks or adverse side effects. Some potential therapeutics developed in the biotechnology industry that initially showed therapeutic promise in early-stage trials have later been found to cause side effects that prevented their further development. Even if the side effects do not preclude setmelanotide from maintaining marketing approval or obtaining additional approvals, undesirable side effects may inhibit market acceptance due to its tolerability versus other therapies. Any of these developments could materially adversely affect our business, financial condition and prospects.

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

- regulatory authorities may request that we withdraw the product from the market or may limit or vary their approval of the product through labeling or other means;
- regulatory authorities may require the addition of labeling statements, such as a “boxed” warning or a contraindication;

- the FDA, the European Commission and other equivalent competent authorities in foreign jurisdictions may require the addition of a Risk Evaluation and Mitigation Strategy, or REMS, or other specific obligations as a condition for marketing authorization due to the need to limit treatment to rare patient populations, or to address safety concerns;

- we may be required to change the way the product is distributed or administered or change the labeling of the product;

- we may be required to conduct additional studies and clinical trials or comply with other post-market requirements to assess possible serious risks;

- we may be required to conduct long term safety follow-up evaluations, including setting up disease and drug based registries;

- we may decide to remove the product from the marketplace;

- we could be sued and held liable for injury caused to individuals exposed to or taking the product; and

- our reputation may suffer.

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

Although we have been granted orphan drug designation for setmelanotide in treating POMC deficiency obesity, LEPR deficiency obesity, Bardet-Biedl syndrome and Alström syndrome in both the United States and the EU, and Prader-Willi syndrome in the EU, we may be unable to obtain orphan drug designation for other uses or to obtain exclusivity in any use. Even with exclusivity, competitors may obtain approval for different drugs that treat the same indications as setmelanotide.

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

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

The exclusivity period in the United States can be extended by six months if the NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. Orphan drug exclusivity may be revoked if the FDA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition. Other potential benefits of orphan drug designation and/or approval of a designated drug include eligibility for: exemption from certain prescription drug user fees, tax credits for certain qualified clinical testing expenses, and waivers from the pediatric assessment requirements of the Pediatric Research Equity Act.

In the EU, orphan drug designation is granted by the European Commission based on a scientific opinion by the EMA's Committee for Orphan Medicinal Products in relation to medicinal products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than five in 10,000

persons in the EU and in relation to which no satisfactory method of diagnosis, prevention, or treatment has been authorized (or the product would be a significant benefit to those affected). Additionally, designation is granted for products intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the medicinal product in the EU would be sufficient to justify the necessary investment in developing the medicinal product.

In addition to a range of other benefits during the development and regulatory review, orphan medicinal products are, upon grant of marketing authorization, entitled to ten years of exclusivity in all EU member states. Marketing authorization may, however, be granted to a similar medicinal product with the same orphan indication during the ten-year period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if the similar product is deemed safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, be reduced to six years if it can be demonstrated on the basis of available evidence that the original orphan medicinal product is sufficiently profitable not to justify maintenance of market exclusivity.

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

We have been granted orphan drug designation for setmelanotide in treating POMC deficiency obesity, LEPR deficiency obesity, BBS and Alström syndrome in both the United States and the EU. We have been granted orphan designation for setmelanotide in treating Prader-Willi syndrome in the EU. There can be no assurance that the FDA or the European Commission will grant such designation for setmelanotide for other uses. In addition, orphan drug designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process.

Even if we obtain orphan drug exclusivity for setmelanotide, that exclusivity may not effectively protect setmelanotide from competition because different drugs can be approved for the same condition. In the United States, even after an orphan drug is approved, the FDA may subsequently approve another drug for the same condition if the FDA concludes that the latter drug is not the same drug or is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. As discussed above, similar rules apply in the EU.

Although we have obtained PRIME designation in the EU and Breakthrough Therapy designation for setmelanotide for the treatment of obesity associated with genetic defects upstream of the MC4R in the leptin-melanocortin pathway, which includes POMC deficiency obesity, LEPR deficiency obesity, Bardet-Biedl syndrome and Alström syndrome in the United States, the FDA may rescind the Breakthrough Therapy Designation and we may be unable to obtain Breakthrough Therapy designation for other uses. In addition, Breakthrough Therapy designation by the FDA may not lead to a faster development, regulatory review or approval process, and it does not increase the likelihood that setmelanotide will receive additional marketing approvals in the United States or a marketing authorization in the EU.

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

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

The PRIME program was launched by the EMA in 2016. PRIME is intended to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimize development plans and speed up evaluation so these medicines can reach patients earlier. In late June 2018, setmelanotide was designated as PRIME by the CHMP. Acknowledging that setmelanotide targets an unmet medical need, the EMA offers enhanced support in the development of the medicinal product through enhanced interaction and early dialogue to optimize our development plans and speed up regulatory evaluation in the EU. As part of this designation, the EMA has provided guidance to us concerning the development of setmelanotide. The PRIME designation does not, however, guarantee that the regulatory review process in the EU will be shorter or less demanding. Neither does the PRIME designation guarantee that the European Commission will grant a marketing authorization for setmelanotide.

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

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

We have entered into a license agreement with Camurus AB, or Camurus, for the use of Camurus' drug delivery technology, FluidCrystal, to formulate once-weekly setmelanotide. This formulation, if successfully developed for setmelanotide, and approved by the FDA and other regulatory authorities, will be delivered subcutaneously, similar to our once-daily formulation, except that we anticipate it will be injected once weekly.

While we have started consultations with regulatory authorities about the potential path for approval of the once-weekly formulation, we cannot yet estimate the requirements for non-clinical and clinical data, manufacturing program, time, cost, and probability of success for approval. Regulatory authorities have limited experience evaluating Camurus' formulations, which further complicates our understanding regarding the information that may be required to obtain approval of a once-weekly formulation.

We received FDA approval of the once-daily formulation in the initial NDA submission for chronic weight management in patients with obesity due to POMC, PCSK1 or LEPR deficiencies, and plan to seek approval of the once-weekly formulation at a later time. While we plan to develop the once-weekly formulation, or to develop other new and useful formulations and delivery technology for setmelanotide, we cannot estimate the probability of success, nor the resources and time needed to succeed. If we are unable to gain approval and utilize the once-weekly formulation, or to develop new formulations, setmelanotide may not achieve significant market acceptance and our business, financial condition and results of operations may be materially harmed.

Our approach to treating patients with MC4R pathway deficiencies requires the identification of patients with unique genetic subtypes, for example, POMC genetic deficiency. The FDA or other equivalent competent authorities in foreign jurisdictions could require the 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, the 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.

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

We have agreements with third-party CROs to provide monitors for and to manage data for our ongoing clinical trials. We rely heavily on these parties for the execution of clinical trials for setmelanotide and control only certain aspects of their activities. As a result, we have less direct control over the conduct, timing and completion of these clinical trials and the management of data developed through the clinical trials than would be the case if we were relying entirely upon our own staff. Communicating with outside parties can also be challenging, potentially leading to mistakes as well as difficulties in coordinating activities. However, we remain responsible for the conduct of these trials and are subject to

enforcement which may include civil and criminal liabilities for any violations of FDA rules and regulations and the comparable foreign regulatory provisions during the conduct of our clinical trials. Outside parties may:

- have staffing difficulties;
- fail to comply with contractual obligations;
- devote inadequate resources to our clinical trials;
- experience regulatory compliance issues;
- undergo changes in priorities or become financially distressed; or
- form more favorable relationships with other entities, some of which may be our competitors.

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

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

Risks Related to the Commercialization of IMCIVREE (setmelanotide)

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

Our ability to commercialize IMCIVREE or any product candidates successfully will depend in part on the extent to which coverage and reimbursement for these product candidates and related treatments will be available from government authorities, private health insurers and other organizations. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels.

Increasing efforts by governmental and third-party payors in the United States and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for newly approved products and, as a result, they may not cover or provide adequate payment. Even if we show improved efficacy or improved convenience of administration with our product candidates, third-party payors may deny or revoke the reimbursement status of our product candidates, if approved, or establish prices for our product candidates at levels that are too low to enable us to realize an appropriate return on our investment. If reimbursement is not available or is available only at limited levels, we may not be able to successfully commercialize setmelanotide or other product candidates, and may not be able to obtain a satisfactory financial return. Further, as we continue to grow as an organization, previously-established prices may no longer be sufficient and could create additional pricing pressure for us.

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

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

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

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

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

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

In order to market IMCIVREE, we must continue to build our sales, marketing, managerial and other non-technical capabilities or make arrangements with third parties to perform these services. Although we have received FDA approval for IMCIVREE, for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to POMC, PCSK1 or LEPR deficiency, we are early in our commercialization efforts and have not yet established a full-scale commercial infrastructure. Therefore, you should not compare us to commercial-stage biotechnology companies, and you should not expect that we will generate substantial revenues or become profitable in the near term. If we are unable to establish adequate sales, marketing and distribution capabilities, whether independently or with third parties, or if we are unable to do so on commercially reasonable terms, our business, results of operations, financial condition and prospects would be materially adversely affected.

We may never receive regulatory approval to market setmelanotide outside of the United States.

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

We may not achieve market acceptance for IMCIVREE, which would limit the revenue that we generate from the sale of setmelanotide.

The commercial success of IMCIVREE will also depend upon the awareness and acceptance of setmelanotide within the medical community, including physicians, patients and third-party payors. If IMCIVREE does not achieve an adequate level of acceptance by patients, physicians and third-party payors, we may not generate sufficient revenue to become or remain profitable. Before granting reimbursement approval, third-party payors may require us to demonstrate that, in addition to treating obesity caused by certain genetic deficiencies affecting the MC4R pathway, IMCIVREE also provides incremental health benefits to patients. Our efforts to educate the medical community and third-party payors

about the benefits of IMCIVREE may require significant resources and may never be successful. All of these challenges may impact our ability to ever successfully market and sell IMCIVREE.

Market acceptance of IMCIVREE will depend on a number of factors, including, among others:

- the ability of IMCIVREE to provide chronic weight management in patients with obesity caused by certain genetic deficiencies affecting the MC4R pathway and, if required by any competent authority in connection with the approval for these indications, to provide patients with incremental health benefits, as compared with other available treatments, therapies, devices or surgeries;
- the complexities of genetic testing, including obtaining genetic results that support patient treatment with IMCIVREE;
- the relative convenience and ease of SC injections as the necessary method of administration of IMCIVREE, including as compared with other treatments for obese patients;
- the prevalence and severity of any adverse side effects associated with IMCIVREE;
- limitations or warnings contained in the labeling approved for IMCIVREE by the FDA or the specific obligations imposed as a condition for marketing authorization imposed by other equivalent competent authorities in foreign jurisdictions, particularly by the European Commission;
- availability of alternative treatments, including a number of obesity therapies already approved or expected to be commercially launched in the near future;
- our ability to increase awareness of these diseases among our target populations through marketing and other cross-functional efforts;
- the size of the target patient population, and the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the ability of IMCIVREE to treat the maximum range of pediatric patients, and any limitations on its indications for use;
- the strength of marketing and distribution support and timing of market introduction of competitive products;
- publicity concerning IMCIVREE or competing products and treatments;
- pricing and cost effectiveness;
- the effectiveness of our sales and marketing strategies;
- our ability to increase awareness of IMCIVREE through marketing efforts;
- our ability to obtain sufficient third-party coverage or reimbursement;
- the willingness of patients to pay out-of-pocket in the absence of third-party coverage; and
- the likelihood that competent authorities in foreign jurisdictions may require development of a REMS as a condition of approval or post-approval, may not agree with our proposed REMS or may impose additional requirements that limit the promotion, advertising, distribution or sales of setmelanotide.

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

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

Currently, IMCIVREE is the only approved treatment for providing chronic weight management in patients with obesity due to POMC, PCSK1 or LEPR deficiencies, and there are no approved treatments for chronic weight management in patients with BBS, Alström syndrome, deficiencies due to a variant in one of the two alleles in the *POMC, PCSK1, or LEPR* genes (HET obesity), SRC1 deficiency obesity, SH2B1 deficiency obesity, MC4R deficiency obesity, or Smith-Magenis syndrome. Bariatric surgery is not a treatment option for these genetic diseases of obesity because the severe obesity and hyperphagia associated with these diseases are considered to be risk factors for bariatric surgery. Based on search results from ClinicalTrials.gov, we are unaware of any competitive products in therapeutic clinical studies for the obesity and hyperphagia caused by upstream MC4R pathway deficiencies specifically, however LG Chem has represented it is in early-stage clinical development of an MC4R agonist. New competitors may emerge which could limit our business opportunity in the future.

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

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

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

- loss of revenue; and
- the inability to successfully commercialize IMCIVREE or any future product candidates, if approved.

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

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

We do not currently have, nor do we plan to acquire, the infrastructure or capability to manufacture our clinical and commercial drug supply internally for setmelanotide, or any future product candidates, for use in the conduct of our preclinical studies and clinical trials, and we lack the internal resources and the capability to manufacture any product candidate on a clinical or commercial scale. The facilities used by our contract manufacturing organizations, or CMOs, to manufacture the active pharmaceutical ingredient, or API, and final drug product must pass inspection by the FDA and other equivalent competent authorities in foreign jurisdictions pursuant to inspections that have been and will be conducted following submission of our NDAs or relevant foreign regulatory submission to the other equivalent competent authorities in foreign jurisdictions. Our failure or the failure of our CMOs to pass preapproval inspection of the manufacturing facilities of setmelanotide could delay the regulatory approval process. In addition, our clinical trials must be conducted with products produced under cGMP regulations. Our failure or the failure of our CROs or CMOs to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process and could also subject us to enforcement action, including civil and criminal penalties. When we import any drugs or drug substances, we would be subject to FDA, United States Department of Agriculture, and U.S. Bureau of Customs and Border Patrol import regulation requirements. Such enforcement for our failure or our CROs or CMOs' failure to comply with these regulations could result in import delays, detention of products, and, depending on criteria such as the history of violative activities, the FDA could place a foreign firm or certain drug substances or products on Import Alert and require that all such drug substances or products be subject to detention without physical examination which could significantly impact the global supply chain for setmelanotide. With the exception of those on the FDA's drug shortage list or properly imported by individuals, the FDCA prohibits the importation of prescription drug products for commercial use if they were manufactured in a foreign country, unless they have been approved or are otherwise authorized to be marketed in the United States and are labeled accordingly.

We currently contract with third parties for the manufacture of setmelanotide and intend to continue to do so in the future. We have entered into process development and manufacturing service agreements with our CMOs, Corden Pharma Brussels S.A., or Corden, (formerly Peptisyntha SA prior to its acquisition by Corden), PolyPeptide Group, Baine L'Alleud, or PPL, Neuland Laboratories, and Recipharm Monts S.A.S. for certain process development and manufacturing services for regulatory starting materials and/or drug substance, or API, and drug product in connection with the manufacture of setmelanotide. Under our agreements, we pay these third parties for services in accordance with the terms of mutually agreed upon work orders, which we may enter into from time to time. We may need to engage additional third-party suppliers to manufacture our clinical and/or commercial, subject to approval, drug supplies. We also have engaged other third parties to assist in, among other things, distribution, post-approval safety reporting and pharmacovigilance activities. We cannot be certain that we can engage third-party suppliers on terms as favorable as those that are currently in place.

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

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

Moreover, as a result of the COVID-19 pandemic, certain of our suppliers and CMOs in Europe may be affected, which could disrupt their activities. As a result, we could face difficulty sourcing key components necessary to produce supply of setmelanotide, which may negatively affect our clinical development and commercialization activities. If the COVID-19 coronavirus further impacts business operations, including our CMOs and suppliers, we could face additional disruption to our supply chain that could affect the supply of drug product for preclinical, clinical trial and commercial use. Additionally, as our CMOs are producers of drug substances and drug products, including vaccines and therapeutics, they could be compelled by a national government, or choose themselves, to shift their resources to the production of a COVID-19 vaccine and/or therapeutics for COVID-19, which could disrupt any scheduled drug substance or drug product batches we may have and may prevent us from obtaining supplies for our programs in a timely manner to meet our development timelines.

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

Risks Related to Our Intellectual Property Rights

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

Our commercial success will depend in part on our success in obtaining and maintaining issued patents and other intellectual property rights in the United States and elsewhere and protecting our proprietary technology. If we do not

adequately protect our intellectual property and proprietary technology, competitors may be able to use our technologies and erode or negate any competitive advantage we may have, which could harm our business and ability to achieve profitability.

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

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

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

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

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

- any of our patents, or any of our pending patent applications, if issued, will include claims having a scope sufficient to protect setmelanotide;
- any of our pending patent applications will issue as patents;
- we will be able to successfully commercialize IMCIVREE before our relevant patents expire;
- we were the first to make the inventions covered by each of our patents and pending patent applications;
- we were the first to file patent applications for these inventions;

- others will not develop similar or alternative technologies that do not infringe our patents;
- any of our patents will be found to ultimately be valid and enforceable;
- any patents issued to us will provide a basis for an exclusive market for our commercially viable products, will provide us with any competitive advantages or will not be challenged by third parties;
- we will develop additional proprietary technologies or product candidates that are separately patentable; or
- our commercial activities or products will not infringe upon the patents of others.

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

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

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

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

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

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

Our success will depend in part on our ability to operate without infringing the intellectual property and proprietary rights of third parties. We cannot assure you that our business, products and methods do not or will not infringe

the patents or other intellectual property rights of third parties. For example, numerous third-party U.S. and non-U.S. patents and pending applications exist that cover melanocortin receptor analogs and methods of using these analogs.

The pharmaceutical industry is characterized by extensive litigation regarding patents and other intellectual property rights. Other parties may allege that setmelanotide or the use of our technologies infringes patent claims or other intellectual property rights held by them or that we are employing their proprietary technology without authorization.

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

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

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

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

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

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

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

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

If we or one of our licensing partners threatened or initiated legal proceedings against a third party to enforce a patent covering setmelanotide, the defendant could claim that the patent covering setmelanotide is invalid and/or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge include alleged failures to meet any one of several statutory requirements, including novelty, non-obviousness and enablement. Grounds for unenforceability assertions include allegations that someone connected with prosecution of the patent withheld material information from the U.S. PTO, or made a misleading statement, during patent prosecution. Third parties may also raise similar claims before administrative

bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, *inter partes* review, post grant review and equivalent proceedings in foreign jurisdictions, for example, opposition proceedings. Such proceedings could result in revocation or amendment of our patents in such a way that they no longer cover setmelanotide or competitive products. The outcome following legal assertions of invalidity and/or unenforceability is unpredictable. With respect to validity, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on setmelanotide. Such a loss of patent protection would have a material adverse impact on our business.

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

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

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

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

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

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

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

We have not yet registered trademarks for a commercial trade name for setmelanotide in the United States and certain foreign jurisdictions and failure to secure such registrations could adversely affect our business.

We have applied for, but not yet received, registered trademark for the commercial trade name IMCIVREE (setmelanotide) and its logo in the United States, and we have obtained trademark protection for IMCIVREE in certain foreign jurisdictions and are pursuing trademark registrations in other jurisdictions. Our trademark applications may be rejected during trademark registration proceedings. Although we would be given an opportunity to respond to those rejections, we may be unable to overcome them. In addition, in the U.S. PTO and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive those proceedings.

Additionally, while the trade name IMCIVREE has been accepted by the FDA, the name IMCIVREE must be approved by the EMA. The objective of the assessment conducted by the EMA is to ensure that there is no risk that the proposed brand name could create a public-health concern or potential safety risk. In particular the proposed brand name should not convey misleading therapeutic or pharmaceutical connotations; be misleading with respect to the composition of the product; or be liable to cause confusion with the brand name of an existing medicinal product in print, handwriting or speech. If the EMA objects to any of our proposed product name, we may be required to expend significant additional resources in an effort to identify a suitable substitute name that would be acceptable to the EMA, qualify under applicable trademark laws and not infringe the existing rights of third parties.

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

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

Because setmelanotide contains active ingredients that the FDA has determined to be a new chemical entity, it has been afforded five years of marketing exclusivity by the FDA. Following the expiration of this marketing exclusivity, the FDA may approve generic products. Manufacturers may seek to launch these generic products following the expiration of the applicable marketing exclusivity period, even if we still have patent protection for setmelanotide. Recent legislation enacted by Congress created, among other things, new causes of action against innovator companies that refuse to offer samples of drugs for purposes of testing and developing generic or biosimilar products or to allow companies to participate in a shared Risk Evaluation and Mitigation Strategy (REMS). Competition that setmelanotide may face from generic versions could materially and adversely impact our future revenue, profitability and cash flows and substantially limit our ability to obtain a return on the investments we have made in setmelanotide.

In the EU, the grant of orphan designation for setmelanotide means that this medicinal product would be entitled, upon grant of marketing authorization by the European Commission, to ten years of exclusivity in all EU member states.

Marketing authorization may, however, be granted to a similar medicinal product with the same orphan indication during the ten year period if we are unable to supply sufficient quantities of setmelanotide. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if the similar product is deemed safer, more effective or otherwise clinically superior to setmelanotide. The period of market exclusivity may, in addition, be reduced to six years if it can be demonstrated on the basis of available evidence that setmelanotide is sufficiently profitable not to justify maintenance of market exclusivity.

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

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

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

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

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

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

Even if we complete the necessary clinical trials, the regulatory and marketing approval process is expensive, time consuming and uncertain and may prevent us from obtaining additional approvals for the commercialization of setmelanotide beyond FDA approval for obesity due to POMC, PCSK1or LEPR deficiencies in the United States. We depend entirely on the success of setmelanotide, and we cannot be certain that we will be able to obtain additional regulatory approvals for, or successfully commercialize, setmelanotide. If we are not able to obtain, or if there are delays in obtaining, required additional regulatory approvals, we will not be able to commercialize setmelanotide in additional indications in the United States or in foreign jurisdictions, and our ability to generate revenue will be materially impaired.

We currently have only one product candidate, setmelanotide, in clinical development, and our business depends entirely on its successful clinical development, regulatory approval and commercialization. Setmelanotide, which is currently approved by FDA for chronic weight management in patients with obesity due to POMC, PCSK1 or LEPR deficiencies, and will require substantial additional clinical development, testing and regulatory approval before we are permitted to commence commercialization in indications beyond those currently approved for IMCIVREE in the United States. The clinical trials, manufacturing and marketing of setmelanotide are subject to extensive and rigorous review and regulation by numerous government authorities in the United States and in other countries where we intend to test and, if approved, market setmelanotide.

Before obtaining regulatory approvals for the commercial sale of any product candidate, we must demonstrate through non-clinical testing and clinical trials that the product candidate is safe and effective for use in each target indication. This process can take many years and approval, if any, may be conditional on post-marketing studies and surveillance, and will require the expenditure of substantial resources beyond our existing cash resources. Of the large number of drugs in development in the United States and in other countries, only a small percentage will successfully complete the FDA regulatory approval process or the equivalent process in foreign jurisdictions and will be commercialized. In addition, we have not discussed all of our proposed development programs with the FDA of the competent authorities of foreign jurisdictions. Accordingly, even if we are able to obtain the requisite financing to continue to fund our development and clinical trials, we cannot assure you that setmelanotide will be successfully developed or commercialized.

In addition, obtaining FDA approval of an NDA for additional indications and the approval of an MAA from the European Commission is a complex, lengthy, expensive and uncertain process, and the FDA, EMA or equivalent competent authorities in foreign jurisdictions may delay, limit or deny approval of setmelanotide for many reasons, including, among others:

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

- we may not be able to demonstrate to the satisfaction of the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions that setmelanotide is safe and effective in treating obesity caused by certain genetic deficiencies affecting the MC4R pathway;

- the results of our clinical trials may not be interpretable or meet the level of statistical or clinical significance required by the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions for marketing approval. For example, the potential unblinding of setmelanotide studies due to easily identifiable AEs may raise the concern that potential bias has affected the clinical trial results;

- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may disagree with the number, size, conduct or implementation of our clinical trials;

- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may require that we conduct additional clinical trials or pre-clinical studies;

- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may not consider that our diagnostic strategy supports approval;

- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may decide that additional assays or data to understand any risks for anti-drug antibodies may need to be available for approval;

- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may decide that the toxicology program, including any parts of carcinogenicity studies that are filed, do not meet the requirements for approval;

- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions or the applicable foreign regulatory agency may identify deficiencies in our chemistry, manufacturing or controls of setmelanotide, or in the commercial production of setmelanotide to support product approval;

- the CROs that we retain to conduct our clinical trials may take actions outside of our control that materially adversely impact our clinical trials;

- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may find the data from preclinical studies and clinical trials insufficient to demonstrate that clinical and other benefits of setmelanotide outweigh its safety risks;

- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may disagree with our interpretation of data from our preclinical studies and clinical trials;

- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may not approve the formulation, labeling or specifications of setmelanotide;

- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may not accept data generated at our clinical trial sites;

- the FDA, the EMA, or the equivalent competent authorities in foreign jurisdictions may require, as a condition of approval, additional preclinical studies or clinical trials, limitations on approved labeling or distribution and use restrictions;

- as part of our NDA approval, we were required to complete certain post-market requirements and commitments, which we may not be able to meet;

- the FDA may require development of a REMS as a condition of additional approvals or may impose additional requirements that limit the promotion, advertising, distribution, or sales of setmelanotide;

- the European Commission may grant only conditional approval marketing authorization or impose specific obligations as a condition for marketing authorization, or may require us to conduct post authorization safety studies as a condition of grant of marketing authorization;

- the FDA or other equivalent competent foreign regulatory agencies may deem our manufacturing processes or our facilities or the facilities of our CMOs inadequate to preserve the identity, strength, quality, purity, or potency of our product; or

- the FDA, the European Commission, or the equivalent competent authorities in foreign jurisdictions may change its approval policies or adopt new regulations and guidance.

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

Disruptions at the FDA and other government agencies caused by funding shortages or global health concerns could hinder their ability to hire, retain or deploy key leadership and other personnel, or otherwise prevent new or modified products from being developed, approved or commercialized in a timely manner or at all, which could negatively impact our business.

The ability of the FDA to review and or approve new products can be affected by a variety of factors, including government budget and funding levels, statutory, regulatory, and policy changes, the FDA's ability to hire and retain key personnel and accept the payment of user fees, and other events that may otherwise affect the FDA's ability to perform routine functions. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of other government agencies that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable. Disruptions at the FDA and other agencies may also slow the time necessary for new drugs and biologics to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including for 35 days beginning on December 22, 2018, the

U.S. government has shut down several times and certain regulatory agencies, such as the FDA, have had to furlough critical FDA employees and stop critical activities.

Separately, in response to COVID-19, on March 10, 2020 the FDA announced its intention to postpone most foreign inspections of manufacturing facilities and products through April 2020, and subsequently, on March 18, 2020, the FDA temporarily postponed routine surveillance inspections of domestic manufacturing facilities. Subsequently, on July 10, 2020 the FDA announced its intention to resume certain on-site inspections of domestic manufacturing facilities subject to a risk-based prioritization system. The FDA intends to use this risk-based assessment system to identify the categories of regulatory activity that can occur within a given geographic area, ranging from mission critical inspections to resumption of all regulatory activities. Regulatory authorities outside the United States may adopt similar restrictions or other policy measures in response to the COVID-19 pandemic. If a prolonged government shutdown occurs, or if global health concerns continue to prevent the FDA or other regulatory authorities from conducting their regular inspections, reviews, or other regulatory activities, it could significantly impact the ability of the FDA or other regulatory authorities to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

Our failure to obtain marketing approval in foreign jurisdictions would prevent setmelanotide from being marketed abroad, and any current or future approvals we have been or may be granted for setmelanotide in the United States would not assure approval of setmelanotide in foreign jurisdictions.

In order to market and sell setmelanotide and any other product candidate that we may develop in the EU and many other jurisdictions, we or our third-party collaborators must obtain separate marketing authorizations and comply with numerous and varying regulatory requirements. The marketing authorization procedure varies among countries and can involve additional testing. The time required to obtain marketing authorization may differ substantially from that required to obtain FDA approval. The marketing authorization process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be sold in that country. We or these third parties may not obtain marketing authorization from competent authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure grant of marketing authorization by competent authorities in other countries or jurisdictions, and grant of marketing authorization by one competent authority outside the United States does not ensure grant of marketing authorization by competent authorities in other countries or jurisdictions or by the FDA. We may not be able to file for marketing authorizations and may not receive necessary marketing authorization to commercialize setmelanotide in any market. Additionally, the United Kingdom's withdrawal from the EU, commonly referred to as Brexit, has resulted in the relocation of the EMA from the United Kingdom to the Netherlands. This relocation has caused, and may continue to cause, disruption in the administrative and medical scientific links between the EMA and the United Kingdom. Medicines and Healthcare products Regulatory Agency, including delays in granting clinical trial authorization or marketing authorization, disruption of importation and export of active substance and other components of new drug formulations, and disruption of the supply chain for clinical trial product and final authorized formulations. The cumulative effects of the disruption to the regulatory framework may add considerably to the development lead time to marketing authorization and commercialization of setmelanotide in the EU and/or the United Kingdom. Any delay in obtaining, or an inability to obtain, any marketing authorization, as a result of Brexit or otherwise, would prevent us from commercializing setmelanotide in the United Kingdom and/or the EU and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek marketing authorization in the United Kingdom and/or EU for setmelanotide, which could significantly and materially harm our business.

The terms of our current and future potential marketing approvals for setmelanotide and ongoing regulation may limit how we manufacture and market setmelanotide, and compliance with such requirements may involve substantial resources, which could materially impair our ability to generate revenue.

Regulatory authorities may impose significant restrictions on setmelanotide's indicated uses or marketing or impose ongoing requirements for potentially costly post approval studies. We and setmelanotide will also be subject to ongoing requirements by the FDA, the European Commission, the EMA, and the competent authorities in the EU member states, governing labeling, packaging, storage, advertising, promotion, marketing, distribution, importation, exportation, post-approval changes, manufacturing, recordkeeping, and submission of safety and other post market information.

Advertising and promotional materials must comply with the FDCA and implementing regulations, and are subject to FDA oversight and post-marketing reporting obligations, in addition to other potentially applicable federal and state laws. The FDA and the other competent foreign authorities have significant post market authority, including, for example, the authority to require labeling changes based on new safety information and to require post market studies or clinical trials to evaluate serious safety risks related to the use of a drug. The FDA also has the authority to require, as part of an NDA or post approval, the submission of a REMS, which may include Elements to Assure Safe Use. Any REMS required by the FDA may lead to increased costs to assure compliance with new post approval regulatory requirements and potential requirements or restrictions on the sale of approved products, all of which could lead to lower sales volume and revenue. The holder of an approved NDA also must submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process, or adding new manufacturers.

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

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

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

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

In addition, a sponsor's responsibilities and obligations under the FDCA and FDA regulations, and those of equivalent foreign regulatory agencies, may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. For example, the results of the 2020 U.S. Presidential Election may impact our business and industry. Namely, the Trump administration took several executive actions, including the issuance of a number of Executive Orders, that could impose

significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine oversight activities such as implementing statutes through rulemaking, issuance of guidance, and review and approval of marketing applications. It is difficult to predict whether or how these orders will be implemented, or whether they will be rescinded and replaced under the Biden administration. The policies and priorities of the new administration are unknown and could materially impact the regulations governing our product candidates. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may be subject to enforcement action and we may not achieve or sustain profitability.

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

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

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

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

In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the ACA. The ACA substantially changed the way healthcare is financed by both governmental and private insurers, and significantly affects the U.S. pharmaceutical industry. Among the provisions of the ACA of importance to our business, including, without limitation, our ability to commercialize and the prices we may obtain for any product candidates that are approved for sale, are the following:

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

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

- expansion of manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs, revising the "average manufacturer price" definition, and extending rebate liability from fee-for-service Medicaid utilization to include the utilization of Medicaid managed care organizations as well as Medicaid managed care;

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

- establishment of the Medicare Part D coverage gap discount program, which requires manufacturers to provide a 70% point-of-sale-discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D;

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

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

Certain provisions of the ACA have been subject to judicial challenges as well as efforts to repeal or replace them or to alter their interpretation or implementation. For example, the Tax Cuts and Jobs Act enacted on December 22, 2017, eliminated the tax-based shared responsibility payment for individuals who fail to maintain minimum essential coverage under section 5000A of the Internal Revenue Code of 1986, as amended, or the Code, commonly referred to as the "individual mandate," effective January 1, 2019. On December 14, 2018, a U.S. District Court Judge in the Northern District of Texas, ruled that the individual mandate is a critical and inseverable feature of the ACA, and therefore, because it was repealed as part of the Tax Act, the remaining provisions of the ACA are invalid as well. On December 18, 2019, the U.S. Court of Appeals for the 5th Circuit upheld the district court's decision that the individual mandate was unconstitutional but remanded the case back to the District Court to determine whether the remaining provisions of the ACA are invalid as well. On March 2, 2020, the U.S. Supreme Court granted the petitions for writs of certiorari to review the case, although it is unclear when a decision will be made or how the Supreme Court will rule. In addition, there may be other efforts to challenge, repeal or replace the ACA, or portions thereof, will affect our business. It is possible that the ACA, as currently enacted or as it may be amended in the future, and other healthcare reform measures that may be adopted in the future, could have a material adverse effect on our industry generally and on our ability to successfully commercialize IMCIVREE or any product candidates, if approved.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. For example, beginning April 1, 2013, Medicare payments for all items and services, including drugs and biologics, were reduced by 2% under the sequestration required by the Budget Control Act of 2011, as amended by the American Taxpayer Relief Act of 2012. Subsequent legislation extended the 2% reduction, on average, to 2029. These reductions will be suspended from May 1, 2020 through December 31, 2020 due to the COVID-19 pandemic. Moreover, the federal government and the individual states in the United States have become increasingly active in developing proposals, passing legislation and implementing regulations designed to control drug pricing, including price or patient reimbursement constraints, discounts, formulary flexibility, marketing cost disclosure and transparency measures. These initiatives may result in additional reductions in Medicare and other healthcare funding and, if we obtain regulatory approvals, may otherwise affect the prices we may obtain for setmelanotide or the frequency with which setmelanotide is prescribed or used if approved.

Additional changes that may affect our business include the expansion of new programs such as Medicare payment for performance initiatives for physicians under the Medicare Access and CHIP Reauthorization Act of 2015, or MACRA, which was fully implemented in 2019. At this time, it is unclear how the introduction of this Medicare quality payment program will impact overall physician reimbursement. The cost of prescription pharmaceuticals in the United States has also been the subject of considerable discussion in the United States. There have been several Congressional inquiries, as well as legislative and regulatory initiatives and executive orders designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products. Members of Congress and the Biden Administration have indicated they will continue to pursue legislative or administrative measures to control prescription drug costs, although the likelihood of such measures being adopted remains uncertain. We cannot predict with certainty what impact any federal or state health reforms will have on us, but such changes could impose new or more stringent regulatory requirements on our activities or result in reduced reimbursement for our products, any of which could adversely affect our business, results of operations and financial condition.

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

The pricing of prescription pharmaceuticals is also subject to governmental control outside the United States. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost effectiveness of setmelanotide to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our ability to generate revenues and become profitable could be impaired. For more details concerning the risks related to pricing and reimbursement in the EU, please refer to the discussion in the risk factor "*The successful commercialization of setmelanotide and our other product candidates will depend in part on the extent to which governmental authorities, private health insurers, and other third-party payors provide coverage and adequate reimbursement levels. Failure to obtain or maintain coverage and adequate reimbursement for setmelanotide or our other product candidates, if approved, could limit our ability to market those products and decrease our ability to generate revenue*" in this Annual Report.

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

We intend to participate in and have certain price reporting obligations to the Medicaid Drug Rebate Program The Medicaid Drug Rebate Program requires participating manufacturers to pay a rebate to each state Medicaid program for covered outpatient drugs that are dispensed to Medicaid beneficiaries and paid for by a state Medicaid. Those rebates

are based on pricing data that must be reported on a monthly and quarterly basis to the CMS, the federal agency that administers the Medicaid Drug Rebate Program. These data include the average manufacturer price and, in the case of innovator products, the best price for each drug which, in general, represents the lowest price available from the manufacturer to any entity in the U.S. in any pricing structure, calculated to include all sales and associated rebates, discounts and other price concessions. Our failure to comply with these price reporting and rebate payment obligations could negatively impact our financial results.

The ACA made significant changes to the Medicaid Drug Rebate Program, as described under the risk factor "*Current and future healthcare reform legislation or regulation may increase the difficulty and cost for us and any future collaborators to obtain marketing approval of and commercialize setmelanotide and may adversely affect the prices we, or they, may obtain and may have a negative impact on our business and results of operations*," above. Congress could enact additional legislation that further increases Medicaid drug rebates or other costs and charges associated with participating in the Medicaid Drug Rebate Program. Additional legislation or the issuance of regulations relating to the Medicaid Drug Rebate Program could have a material adverse effect on our results of operations.

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

HRSA issued a final regulation regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities, which became effective on January 1, 2019. It remains uncertain how HRSA will apply its enforcement authority under the new regulation. HRSA also has implemented reporting requirement pursuant to which participating manufacturers are required to report the 340B ceiling prices for their drugs to HRSA every quarter. In addition, legislation may be introduced that, if passed, would further expand the 340B program to additional covered entities or would require participating manufacturers to agree to provide 340B discounted pricing on drugs used in an inpatient setting.

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

CMS and the Department of Health & Human Services Office of Inspector General have pursued manufacturers that were alleged to have failed to report these data to the government in a timely manner. Governmental agencies may

also make changes in program interpretations, requirements or conditions of participation, some of which may have implications for amounts previously estimated or paid. We cannot assure you that any submissions we are required to make under the Medicaid Drug Rebate Program and consequently the 340B program will not be found to be incomplete or incorrect.

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

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

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

The FDA and other regulatory agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses.

In the United States, the FDA strictly regulates marketing, labeling, advertising and promotion of prescription drugs. These regulations include standards and restrictions for direct-to-consumer advertising, industry-sponsored scientific and educational activities, promotional activities involving the internet and off-label promotion. Any regulatory approval that the FDA grants is limited to those specific diseases and indications for which a product is deemed to be safe and effective by the FDA. For example, the FDA-approved label for IMCIVREE is limited to chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to POMC, PCSK1, or LEPR deficiency confirmed by genetic testing demonstrating variants in *POMC, PCSK1, or LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance. In addition to the FDA approval required for new formulations, any new indication for an approved product also requires FDA approval. If we are not able to obtain FDA approval for any desired future indications for our drugs and drug candidates, our ability to effectively market and sell our products may be reduced and our business may be adversely affected.

While physicians in the United States may choose, and are generally permitted, to prescribe drugs for uses that are not described in the product's labeling and for uses that differ from those tested in clinical trials and approved by the regulatory authorities, our ability to promote the products is narrowly limited to those indications that are specifically approved by the FDA. These "off-label" uses are common across medical specialties and may constitute an appropriate treatment for some patients in varied circumstances. For example, we are actively evaluating IMCIVREE in subjects with other forms of obesity caused by defects in the MCR4 pathway. We are not currently permitted to, and do not, market or promote setmelanotide for these uses.

Regulatory authorities in the United States generally do not regulate the behavior of physicians in their choice of treatments. Regulatory authorities do, however, restrict communications by pharmaceutical companies on the subject of off-label use. Although recent court decisions suggest that certain off-label promotional activities may be protected under the First Amendment, the scope of any such protection is unclear. If our promotional activities fail to comply with the FDA's regulations or guidelines, we may be subject to warnings from, or enforcement action by, these authorities. In addition, our failure to follow FDA rules and guidelines relating to promotion and advertising may cause the FDA to issue warning letters or untitled letters, bring an enforcement action against us, suspend or withdraw an approved product from the market, require a recall or institute fines or civil fines, or could result in disgorgement of money, operating restrictions, injunctions or criminal prosecution, any of which could harm our reputation and our business.

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

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

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

- The United States federal healthcare Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, or receiving remuneration, (anything of value), directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, lease order or arranging for or recommending the purchase, lease or order of any good or service for which payment may be made, in whole or in part, by federal healthcare programs such as Medicare and Medicaid. This statute has been interpreted to apply to arrangements between pharmaceutical companies on one hand and prescribers, purchasers, formulary managers, and patients on the other. Liability under the Anti-Kickback Statute may be established without proving actual knowledge of the statute or specific intent to violate it. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. Although there are a number of statutory exceptions and regulatory safe harbors to the federal Anti-Kickback Statute protecting certain common business arrangements and activities from prosecution or regulatory sanctions, the exceptions and safe harbors are drawn narrowly. Practices that involve remuneration to those who prescribe, purchase, or recommend pharmaceutical and biological products, including certain discounts, or engaging such individuals or patients as consultants, advisors, or speakers, may be subject to scrutiny if they do not fit squarely within an exception or safe harbor. Our practices may not in all cases meet all of the criteria for safe harbor protection from anti-kickback liability. Moreover, there are no safe harbors for many common practices, such as educational and research grants, charitable donations, product and patient support programs. In October 2019, the federal government

published a proposed regulation creating new safe harbors for, among other things, certain value-based arrangements and patient engagement tools, and that modifies and clarifies the scope of existing safe harbors for warranties and personal service agreements. The impact of the proposed regulation on our current or contemplated operations is not clear even if the proposed regulation is finalized.

- The federal civil False Claims Act prohibits individuals or entities from, among other things, knowingly presenting, or causing to be presented a false or fraudulent claim for payment of government funds, or knowingly making, using or causing to made or used a false record or statement material to an obligation to pay money to the government or knowingly concealing or knowingly and improperly avoiding, decreasing or concealing an obligation to pay money to the federal government. Actions under the False Claims Act may be brought by the Attorney General or as a qui tam action by a private individual in the name of the government. Such private individuals may share in amounts paid by the entity to the government in recovery or settlement. Many pharmaceutical manufacturers have been investigated and have reached substantial financial settlements with the federal government under the civil False Claims Act for a variety of alleged improper activities including causing false claims to be submitted as a result of the marketing of their products for unapproved and thus non-reimbursable uses, inflating prices reported to private price publication services which are used to set drug payment rates under government healthcare programs, and other interactions with prescribers and other customers including those that may have affected their billing or coding practices and submission to the federal government. The government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. False Claims Act liability is potentially significant in the healthcare industry because the statute provides for treble damages and significant mandatory penalties per false or fraudulent claim or statement for violations. Because of the potential for large monetary exposure, healthcare and pharmaceutical companies often resolve allegations without admissions of liability for significant and material amounts to avoid the uncertainty of treble damages and per claim penalties that may be awarded in litigation proceedings. Settlements may require companies to enter into corporate integrity agreements with the government, which may impose substantial costs on companies to ensure compliance. Pharmaceutical and other healthcare companies also are subject to other federal false claims laws, including, among others, federal criminal healthcare fraud and false statement statutes that extend to non-government health benefit programs.

- The federal Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program, including private third-party payors, and also imposes obligations, with respect to safeguarding the privacy, security and transmission of individually identifiable health information. Penalties for failure to comply with a requirement of HIPAA vary significantly and include civil monetary penalties as well as criminal penalties for knowingly obtaining or disclosing individually identifiable health information in violation of HIPAA. The criminal penalties increase if the wrongful conduct involves false pretenses or the intent to sell, transfer or use identifiable health information for commercial advantage, personal gain or malicious harm. HIPAA also prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement or representation, or making or using any false writing or document knowing the same to contain any materially false, fictitious or fraudulent statement or entry in connection with the delivery of or payment for healthcare benefits, items or services. Similar to the federal healthcare Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it to have committed a violation. Pharmaceutical and other healthcare companies also are subject to state laws governing the privacy and security of health, genetic, sensitive condition and personally identifiable information, many of which enable a state attorney general to bring actions and provide private rights of action to consumers as enforcement mechanisms. There is also heightened sensitivity for minors' information, which may be subject to additional protections. Federal regulators, state attorneys general, and plaintiffs' attorneys have been and will likely continue to be active in this space.

- The federal Physician Payments Sunshine Act, implemented as the Open Payments Program, requires certain manufacturers of drugs, devices, biologics and medical supplies to report payments and other transfers of

value to physicians for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report annually to the United States Department of Health and Human Services, Centers for Medicare and Medicaid Services, information related to physicians (defined to include doctors, dentists, optometrists, podiatrists, and chiropractors) and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Beginning in 2022, applicable manufacturers also will be required to report information regarding payments and transfers of value provided to physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, and certified nurse-midwives. Manufacturers must submit reports on or before the 90th day of each calendar year disclosing reportable payments made in the previous calendar year.

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

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

Ensuring that our business arrangements and interactions with healthcare professionals, third-party payors, patients and others comply with applicable healthcare laws and regulations will require substantial resources. Various state and federal regulatory and enforcement agencies continue actively to investigate violations of health care laws and regulations, and the United States Congress continues to strengthen the arsenal of enforcement tools. The BBA of 2018 increased the criminal and civil penalties that can be imposed for violating certain federal health care laws, including the Anti-Kickback Statute.

It is possible that governmental authorities will conclude that our business practices do not comply with current or future statutes, regulations or case law involving applicable fraud and abuse, privacy, or other healthcare laws and regulations. If our operations, including our engagements with healthcare professionals, researchers and patients, or our disease awareness and/or patient identification initiatives including genetic testing programs, or anticipated activities to be conducted by our field teams, were found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to costly investigations, significant civil, criminal and administrative monetary penalties, imprisonment, damages, fines, disgorgement, exclusion from government funded healthcare programs, such as Medicare and Medicaid, contractual damages, diminished profits and future earnings, and the curtailment or restructuring of our operations, any of which could substantially disrupt our operations or financial results. Although compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. Any action against us for violation of these laws or regulations, even if we successfully defend against it, could cause us to incur significant legal expenses and generate negative publicity, which could harm our financial condition and divert our management's attention from the operation of our business.

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

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with the regulations of the FDA and applicable non-U.S. regulators, provide accurate

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

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

We are subject to U.S. data protection laws and regulations, for example, laws and regulations that address privacy and data security, at both the federal and state levels. The legislative and regulatory landscape for data protection continues to evolve, and in recent years there has been an increasing focus on privacy and data security issues. Numerous federal and state laws, including state data breach notification laws, state health information privacy laws, state genetic privacy laws, and federal and state consumer protection laws, including, for example, Section 5 of the Federal Trade Commission Act of 1914, as amended, and the CCPA, govern the collection, use, and disclosure and protection of certain health-related and other personal information. Failure to comply with data protection laws and regulations could result in government enforcement actions and create liability for us, which could include civil and/or criminal penalties, private litigation and/or adverse publicity that could negatively affect our operating results and business. In addition, we may obtain health information from third parties, such as research institutions with which we collaborate, that are subject to privacy and security requirements under HIPAA. Although we are not directly subject to HIPAA, other than potentially with respect to providing certain employee benefits, we could be subject to criminal penalties if we knowingly obtain or disclose individually identifiable health information maintained by a HIPAA covered entity in a manner that is not authorized or permitted by HIPAA. In addition, state laws govern the privacy and security of health, research and genetic information in specified circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. Some of our research activities involve minors, which may be subject to additional laws and can require specialized consent processes, privacy protections, and compliance procedures.

The EU, United Kingdom, Switzerland and other countries have also adopted data protection laws and regulations, which impose significant compliance obligations. In the EU, the collection and use of personal data, including health and genetic data, is governed by the provisions of the General Data Protection Regulation, or GDPR. The GDPR became effective on May 25, 2018, repealing the Data Protection Directive and increasing our responsibility and liability in relation to the processing of personal data of EU subjects. Fines for certain breaches of the GDPR are significant, up to the greater of 20 million Euros or 4 % of total global annual turnover. In addition to the foregoing, a breach of the GDPR could result in regulatory investigations, reputational damage, orders to cease/change our processing of our data, enforcement notices, and/or assessment notices (for a compulsory audit). We may also face civil claims including representative actions and other class action type litigation (where individuals have suffered harm), potentially amounting to significant compensation or damages liabilities, as well as associated costs, diversion of internal resources, and reputational harm. Additionally, from 1 January 2021, we are subject to the GDPR and also the United Kingdom GDPR, which, together with the amended United Kingdom Data Protection Act 2018, retains the GDPR in United Kingdom national law following Brexit. The United Kingdom GDPR mirrors the fines under the GDPR, e.g. fines up to the greater of €20 million (£17.5 million) or 4% of global turnover. The relationship between the United Kingdom and the European Union in relation to certain aspects of data protection law remains unclear, and it is unclear how United Kingdom data

protection laws and regulations will develop in the medium to longer term. These changes will lead to additional costs and increase our overall risk exposure.

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

With respect to the transfer of personal data out of the EU and the United Kingdom, the GDPR and the United Kingdom GDPR provides that the transfer of personal data to countries that are not considered by the European Commission to provide an adequate level of data protection, including the United States, is permitted only on the basis of complying with specific legal steps, a number of which are subject to legal challenges. Most recently, on July 16, 2020, the Court of Justice of the European Union ("CJEU") invalidated the EU-US Privacy Shield Framework ("Privacy Shield") under which personal data could be transferred from the EEA to US entities who had self-certified under the Privacy Shield scheme. These recent developments may require us to review and amend the legal mechanisms by which we make and/or receive personal data transfers to/in the U.S. As supervisory authorities issue further guidance on personal data export mechanisms, including circumstances where the standard contractual clauses cannot be used, and/or start taking enforcement action, we could suffer additional costs, complaints and/or regulatory investigations or fines, and/or if we are otherwise unable to transfer personal data between and among countries and regions in which we operate, it could affect the manner in which we provide our services, the geographical location or segregation of our relevant systems and operations, and could adversely affect our financial results. In addition, the United Kingdom's withdrawal from the European Union means that the United Kingdom will become a "third country" for the purposes of data transfers from the European Union to the United Kingdom following the expiration of the four to six-month personal data transfer grace period (from 1 January 2021) set out in the EU and United Kingdom Trade and Cooperation Agreement, unless a relevant adequacy decision is adopted in favor of the United Kingdom (which would allow data transfers without additional measures). These changes may require us to find alternative solutions for the compliant transfer of personal data into the United Kingdom.

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

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

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

- our customers' ability to obtain reimbursement for setmelanotide in foreign markets;
- our inability to directly control commercial activities because we are relying on third parties;
- the burden of complying with complex and changing foreign regulatory, tax, accounting and legal requirements;
- different medical practices and customs in foreign countries affecting acceptance in the marketplace;

- import or export licensing requirements;
- longer accounts receivable collection times;
- longer lead times for shipping;
- language barriers for technical training;
- reduced protection of intellectual property rights in some foreign countries;
- foreign currency exchange rate fluctuations; and
- the interpretation of contractual provisions governed by foreign laws in the event of a contract dispute.

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

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

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

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

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

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

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

Following a national referendum and enactment of legislation by the government of the United Kingdom, the United Kingdom formally withdrew from the EU on January 31, 2020 (commonly referred to as "Brexit") and entered into a transition period which ended on December 31, 2020. Since the expiry of the transition period, the United Kingdom operates under a distinct regulatory regime. EU pharmaceutical laws only apply to the United Kingdom in respect of Northern Ireland (as laid out in the Protocol on Ireland and Northern Ireland). Since January 1, 2021, the EU laws which have been transposed into UK law through secondary legislation continue to be applicable as "retained EU law". As there is no general power to amend these regulations, the UK government has introduced a new Medicines and Medical Devices Bill which seeks to address regulatory gaps through implementing regulations and delegated powers covering the fields of human medicines, clinical trials of human medicines, veterinary medicines and medical devices. The purpose of the bill is to enable the existing UK regulatory frameworks to be updated. Although regulatory authorities in the UK have indicated in the bill that new UK rules will closely align with EU laws, detailed proposals are yet to be published. Significant political and economic uncertainty therefore remains about how much the relationship between the United Kingdom and EU will differ as a result of the United Kingdom's withdrawal.

On December 24, 2020, the United Kingdom and the EU announced that they had agreed to the terms of their future trading relationship in the EU—United Kingdom Trade and Cooperation Agreement ("TCA"), which has been provisionally applicable since January 1, 2021, but which awaits the final agreement of the remaining 27 EU member states. While agreement on the terms of the TCA has avoided a " no deal" Brexit scenario, and provides in principle for quota- and tariff-free trading of goods, it is nevertheless expected that the TCA will result in the creation of non-tariff barriers (such as increased shipping and regulatory costs and complexities) to the trade in goods between the United Kingdom and the EU. Further, the TCA does not provide for the continued free movement of services between the United Kingdom and the EU and imposes additional restrictions on the free movement of people between the United Kingdom and the EU. The TCA includes provisions affecting pharmaceutical companies such as customs and tariffs in relation to healthcare products and provides for the mutual recognition of Good Manufacturing Practice (GMP) inspections of manufacturing facilities for medicinal products and GMP documents issued. It is important to note however that significant regulatory gaps still exist and the TCA does not contain wholesale mutual recognition of United Kingdom and EU pharmaceutical regulations and product standards, for example in relation to batch testing and pharmacovigilance, which remain subject to further bilateral discussions.

The United Kingdom's withdrawal from the EU and the associated uncertainty has had and may continue to have a significant adverse effect on global economic conditions and the stability of global financial markets, and could significantly reduce global market liquidity and restrict the ability of key market participants to operate in certain financial markets. Asset valuations, currency exchange rates and credit ratings may be especially subject to increased market volatility. Any of these factors could have a significant adverse effect on our business, financial condition, results of operations and prospects.

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

Risks Related to Employee Matters and Managing Growth

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

We are highly dependent on our executive leadership team. We have employment agreements with these individuals but any individual may terminate his or her employment with us at any time. The loss of their services might impede the achievement of our research, development and commercialization objectives. We also do not have any key-person life insurance on any of these key employees. We rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us and may not be subject to non-compete agreements. Recruiting and retaining qualified scientific personnel and sales and marketing personnel will also be critical to our success. We may not be able to attract and retain these personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific personnel from universities and research institutions. Failure to succeed in clinical trials may make it more challenging to recruit and retain qualified scientific personnel.

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

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

The physical expansion of our operations may lead to significant costs and may divert financial resources from other projects, such as the development of setmelanotide. Many of our suppliers and collaborative and clinical trial relationships are located outside the United States, and we may in the future seek to hire employees located outside of the United States. Accordingly, our business may become subject to economic, political, regulatory and other risks associated with international operations, such as compliance with tax, employment, immigration and labor laws for employees living or traveling abroad, workforce uncertainty in countries where labor unrest is more common than in the United States, as well as difficulties associated with staffing and managing international operations, including differing labor relations. Any of these factors could materially affect our business, financial condition and results of operations. Our future financial performance and our ability to commercialize setmelanotide, if approved, and compete effectively will depend, in part, on our ability to effectively manage the future development and expansion of our company.

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

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

employee error, malfeasance or other disruptions, natural disasters, terrorism and telecommunication and electrical failures. Any such attack, incident or breach could compromise our networks and the information stored there could be accessed, publicly disclosed, lost, corrupted or stolen. Further, attacks upon information technology systems are increasing in their frequency, levels of persistence, sophistication and intensity, and are being conducted by sophisticated and organized groups and individuals with a wide range of motives and expertise. As a result of the COVID-19 pandemic, we may also face increased cybersecurity risks due to our reliance on internet technology and the number of our employees who are working remotely, which may create additional opportunities for cybercriminals to exploit vulnerabilities. Furthermore, because the techniques used to obtain unauthorized access to, or to sabotage, systems change frequently and often are not recognized until launched against a target, we may be unable to anticipate these techniques or implement adequate preventative measures. We may also experience security breaches that may remain undetected for an extended period. The legislative and regulatory landscape for privacy and data protection continues to evolve, and there has been an increasing amount of focus on privacy and data protection issues with the potential to affect our business, including recently enacted laws in a majority of states requiring security breach notification, some also require implementation of reasonable security measures and provide a private right of action in the event of a breach. Costs of breach response, mitigation, investigation, remediation, notice and ongoing assessments can be considerable. Thus, any access, disclosure, damage or other loss of information, including our data being breached at our partners or third-party providers, could result in legal claims or proceedings and liability under state, federal and international privacy laws, disruption of our operations, and damage to our reputation, which could adversely affect our business.

If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our programs. For example, the loss of clinical trial data for setmelanotide or other product candidates could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of or damage to our data or applications or other data or applications relating to our technology or product candidates, or inappropriate disclosure of confidential or proprietary information, we could incur liabilities and the further development of setmelanotide and our product candidates could be delayed.

Risks Related to Our Common Stock

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

Our executive officers and directors and their respective affiliates, in the aggregate, hold shares representing approximately 15.7% of our outstanding voting stock as of December 31, 2020. As a result, if these stockholders were to choose to act together, they would be able to significantly influence all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these stockholders could significantly influence elections of directors, any amendments of our organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may feel are in your best interest as one of our stockholders.

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

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

to receive a premium for their shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

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

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

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

Our quarterly operating results may fluctuate significantly.

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

- variations in the level of expenses related to our development programs;
- addition or termination of clinical trials;

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

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

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

Under the Code, a corporation is generally allowed a deduction for net operating losses, or NOLs, carried over from a prior taxable year, and can use such NOLs to offset future taxable income, if any, until such losses are used or, for NOLs arising in taxable years ending on or before December 31, 2017, until such NOLs expire. Other unused tax attributes, such as research tax credits may also be carried forward to offset future taxable income, if any, until such attributes are used or expire. As of December 31, 2020, we had approximately $382.3 million and $351.2 million of unused federal and state NOL carryforwards, respectively, and approximately $8.1 million and $2.8 million of unused federal and state carryforwards of research tax credits, respectively. Of the federal NOL carryforwards at December 31, 2020, $309.1 million can be carried forward indefinitely, while $73.2 million will begin to expire in 2033. Additionally, as of December 31, 2020, we had federal orphan drug credits related to qualifying research of $10.1 million.

If a corporation undergoes an "ownership change," very generally defined as a greater than 50% change by value in its equity ownership by certain shareholders or groups of shareholders over a rolling three-year period, Sections 382 and 383 of the Code limit the corporation's ability to use carryovers of its pre-change NOLs, credits and certain other tax attributes to reduce its tax liability for periods after the ownership change. Our issuance of common stock pursuant to prior public offerings may have resulted in a limitation under Code Sections 382 and 383, either separately or in combination with certain prior or subsequent shifts in the ownership of our common stock. Future changes in our stock ownership, some of which are outside of our control, could also result in an ownership change under Sections 382 and 383 of the Code. In addition, for taxable years beginning after December 31, 2020, utilization of federal NOLs generated in tax years beginning after December 31, 2017 are limited to a maximum of 80% of the taxable income for such year, after taking into account utilization of NOLs generated in years beginning before January 1, 2018 and determined without regard to such NOL deduction. Further regulatory changes could also limited our ability to utilize our NOLs. As a result, our ability to use carryovers of NOLs and credits to reduce our future U.S. federal income tax liability may be subject to limitations. This could result in increased U.S. federal income tax liability for us if we generate taxable income in a future period. Limitations on the use of NOLs and other tax attributes could also increase our state tax liability. Any such limitation could have a material adverse effect on our results of operations in future years. We have not completed a study to assess whether an ownership change for purposes of Section 382 or 383 has occurred, or whether there have been multiple ownership changes since our inception, due to the significant costs and complexities associated with such study.

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

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

Sales of our common stock in the public market, or the perception that these sales could occur, could cause the market price of our common stock to decline significantly. As of December 31, 2020, we had 44,235,903 shares of common stock outstanding.

The holders of an aggregate of approximately 6.9 million shares of our common stock, or approximately 16% of our total outstanding common stock as of December 31, 2020, are entitled to rights with respect to the registration of their shares under the Securities Act, subject to specified conditions, until such shares can otherwise be sold without restriction under Rule 144 or until the rights terminate pursuant to the terms of the investors' rights agreement between us and such holders. We have also registered and intend to continue to register all shares of common stock that we may issue under our equity compensation plans. Once we register these shares under the Securities Act, the shares become freely tradable without restriction under the Securities Act, except for shares purchased by affiliates. Any sales of securities by these stockholders could have a material adverse effect on the trading price of our common stock.

In addition, 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 the prospectus supplement filed in connection with our February 2021 public offering, 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.

We ***are no longer an "emerging growth company" and, as a result, are subject to certain enhanced disclosure requirements.***

Because the market value of our common stock held by non-affiliates exceeded $700.0 million as of June 30, 2020, among other things, we no longer qualified as an emerging growth company as of December 31, 2020. As a result, commencing January 1, 2021, we are subject to certain requirements that apply to other public companies but did not previously apply to us due to our status as an emerging growth company, such as the auditor attestation requirements under Section 404 of the Sarbanes Oxley Act of 2002, as amended. Compliance with these enhanced disclosure requirements will increase our costs and could negatively affect our results of operations and financial condition.

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

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

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

We have never declared or paid any cash dividends on our common stock and do not currently intend to do so in the foreseeable future. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends in the foreseeable future. Therefore, the success of an investment in shares of our common stock will depend upon any future appreciation in their value. There

is no guarantee that shares of our common stock will appreciate in value or even maintain the price at which you purchased them.

Provisions in our certificate of incorporation and bylaws and Delaware law might discourage, delay or prevent a change in control of our company or changes in our management and, therefore, depress the market price of our common stock.

Our certificate of incorporation and bylaws contain provisions that could depress the market price of our common stock by acting to discourage, delay or prevent a change in control of our company or changes in our management that the stockholders of our company may deem advantageous. These provisions, among other things:

- establish a classified board of directors so that not all members of our board are elected at one time;
- permit only the board of directors to establish the number of directors and fill vacancies on the board;
- provide that directors may only be removed "for cause" and only with the approval of two-thirds of our stockholders;
- authorize the issuance of "blank check" preferred stock that our board could use to implement a stockholder rights plan (also known as a "poison pill");
- eliminate the ability of our stockholders to call special meetings of stockholders;
- prohibit stockholder action by written consent, which requires all stockholder actions to be taken at a meeting of our stockholders;
- prohibit cumulative voting;
- authorize our board of directors to amend the bylaws;
- establish advance notice requirements for nominations for election to our board or for proposing matters that can be acted upon by stockholders at annual stockholder meetings; and
- require a super-majority vote of stockholders to amend some provisions described above.

In addition, Section 203 of the General Corporation Law of the State of Delaware, or the DGCL, prohibits a publicly-held Delaware corporation from engaging in a business combination with an interested stockholder, generally a person which together with its affiliates owns, or within the last three years has owned, 15% of our voting stock, for a period of three years after the date of the transaction in which the person became an interested stockholder, unless the business combination is approved in a prescribed manner.

Any provision of our certificate of incorporation, bylaws or Delaware law that has the effect of delaying or preventing a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our capital stock and could also affect the price that some investors are willing to pay for our common stock.

Our certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for substantially all disputes between us and our stockholders and our bylaws designate the federal district courts of the United States as the exclusive forum for actions arising under the Securities Act, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for: (i) any derivative action or proceeding brought on our behalf; (ii) any action asserting a claim of breach of fiduciary duty; (iii) any action asserting a claim against us arising under the DGCL, our certificate of incorporation or our

bylaws; and (iv) any action asserting a claim against us that is governed by the internal affairs doctrine. In addition, our bylaws provide that the federal district courts of the United States are the exclusive forum for any complaint raising a cause of action arising under the Securities Act. Any person or entity purchasing or otherwise acquiring any interest in any of our securities shall be deemed to have notice of and consented to the provisions of our certificate of incorporation and bylaws described above. These exclusive-forum provisions may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage lawsuits against us and our directors, officers and other employees. If a court were to find these provisions of our certificate of incorporation or bylaws to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving the dispute in other jurisdictions, which could seriously harm our business.

General Risk Factors

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

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

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

Our stock began trading on the Nasdaq Global Market in October 2017 and we can provide no assurance that we will be able to continue to maintain an active trading market on the Nasdaq Global Market or any other exchange in the future. If an active market for our common stock is not maintained, it may be difficult for our stockholders to sell shares without depressing the market price for the shares or at all. An inactive market may also impair our ability to raise capital by selling shares and may impair our ability to acquire other businesses, applications or technologies using our shares as consideration.

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

The trading market for our common stock depends in part on the research and reports that securities or industry analysts publish about us, our business, our market or our competitors. We do not control these analysts. If we lose securities or industry analysts coverage of our company, the trading price for our stock would be negatively impacted. If one or more of the analysts who covers us downgrades our stock, our stock price would likely decline. If one or more of these analysts issues unfavorable commentary or ceases to cover us or fails to regularly publish reports on us, interest in our stock could decrease, which could cause our stock price or trading volume to decline.

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

We may seek additional capital through a combination of private and public equity offerings, debt financings, collaborations and strategic and licensing arrangements. To the extent that we raise additional capital through the sale of common stock or securities convertible or exchangeable into common stock, a stockholder's ownership interest in our company will be diluted. In addition, the terms of any such securities may include liquidation or other preferences that materially adversely affect the rights of our stockholders. Debt financing, if available, would increase our fixed payment obligations and may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through collaboration, strategic partnerships and licensing arrangements with third parties, we may have to relinquish valuable

rights to setmelanotide, our intellectual property or future revenue streams, or grant licenses on terms that are not favorable to us.

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

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

We have incurred and will continue to incur substantial costs as a result of operating as a public company, our management will continue to devote substantial time to new compliance initiatives and corporation governance policies, and we will need to hire additional qualified accounting and financial personnel with appropriate public company experience.

As a public company, and particularly now that we are no longer an emerging growth company, we have incurred and will continue to incur significant legal, accounting and other expenses. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of the Nasdaq Global Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will continue to devote a substantial amount of time to these compliance initiatives and we will need to continue to hire additional accounting and financial personnel with appropriate public company experience and technical accounting knowledge. Even if we are able to hire appropriate personnel, our existing operating expenses and operations will be impacted by the direct costs of their employment and the indirect consequences related to the diversion of management resources from product development efforts. Moreover, these rules and regulations will continue to increase our legal and financial compliance costs and make some activities more time-consuming and costly.

These rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in future uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

If we fail to maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results or prevent fraud. As a result, stockholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our common stock.

Effective internal control over financial reporting is necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, is designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause us to fail to meet our reporting obligations. In addition, any testing by us conducted in connection with Section 404, or any testing by our independent registered public accounting firm, may reveal deficiencies in our internal control over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our financial statements or identify other areas for further attention or improvement.

Pursuant to Section 404, we are required to furnish a report by our management on our internal control over financial reporting. To continue to achieve compliance with Section 404, we continue to be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control

processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude that our internal control over financial reporting is effective as required by Section 404.

In addition, because we no longer qualify as an emerging growth company as of December 31, 2020, we are required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. If we are unable to maintain effective internal control over financial reporting, we may not have adequate, accurate or timely financial information, our independent registered public accounting firm may issue a report that is adverse, and we may be unable to meet our reporting obligations as a public company or comply with the requirements of the SEC or Section 404. This could result in a restatement of our financial statements, the imposition of sanctions, including the inability of registered broker dealers to make a market in our common stock, or investigation by regulatory authorities. Any such action or other negative results caused by our inability to meet our reporting requirements or comply with legal and regulatory requirements or by disclosure of an accounting, reporting or control issue could adversely affect the trading price of our securities and our business. Material weaknesses in our internal control over financial reporting could also reduce our ability to obtain financing or could increase the cost of any financing we obtain. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

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

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

Item 3. Legal Proceedings

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

Item 4. Mine Safety Disclosures

Not applicable.

PART II

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

Our common stock has been listed on The Nasdaq Global Market under the symbol "RYTM" since October 5, 2017. Prior to that date, there was no public trading market for our common stock.

Holders of Common Stock

As of February 19, 2021, there were 20 holders of record of our common stock. This number does not reflect beneficial owners whose shares are held in street name.

Securities Authorized for Issuance Under Equity Compensation Plans

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

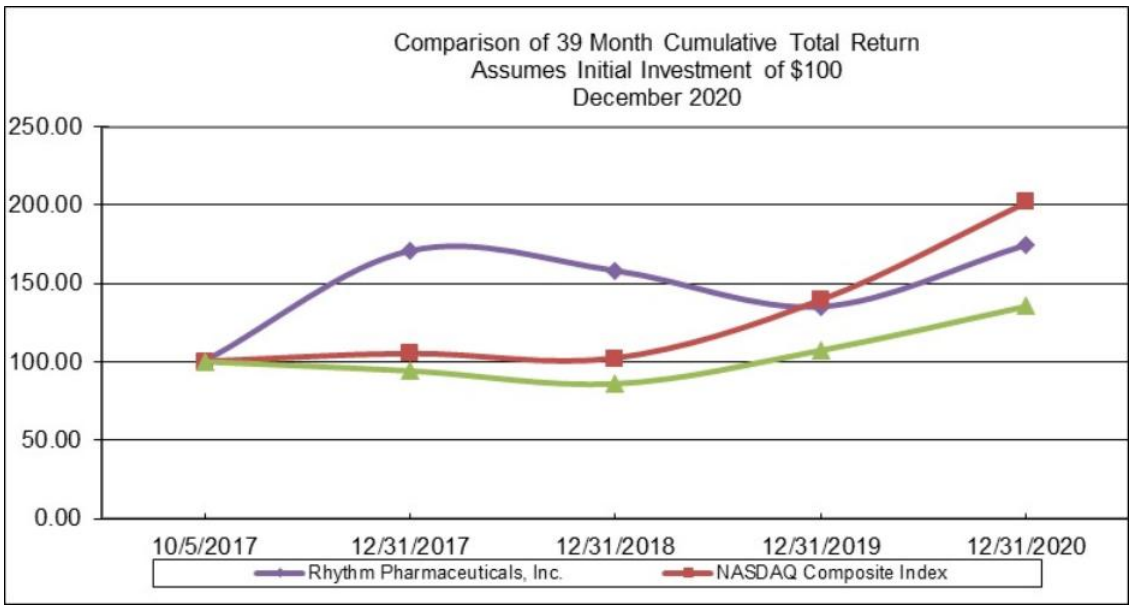
Dividend Policy

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

Performance Graph

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

The following graph shows the total stockholder return of an investment of $100 in cash at market close on October 5, 2017 (the first day of trading of our common stock) through December 31, 2020 for (1) our common stock, (2) the Nasdaq Composite Index (U.S.) and (3) the Nasdaq Biotechnology Index. Pursuant to applicable Securities and Exchange Commission rules, all values assume reinvestment of the full amount of all dividends, however no dividends have been declared on our common stock to date. The stockholder return shown on the graph below is not necessarily indicative of future performance, and we do not make or endorse any predictions as to future stockholder returns.



Recent Sales of Unregistered Securities

None.

Purchases of Equity Securities by the Issuer and Affiliated Purchasers

None.

Item 6. Selected Financial Data

Not Applicable.

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

You should read the following discussion and analysis of our financial condition and results of operations together with our financial statements and related notes appearing elsewhere in this Annual Report. In addition to historical information, this discussion and analysis contains forward-looking statements that involve risks, uncertainties and assumptions. Our actual results may differ materially from those anticipated in these forward-looking statements as

a result of certain factors. We discuss factors that we believe could cause or contribute to these differences below and elsewhere in this report, including those set forth under Item 1A. "Risk Factors" and under "Cautionary Note Regarding Forward-Looking Statements" in this Annual Report. Discussion and analysis of our 2019 fiscal year specifically, as well as the year-over-year comparison of our 2019 financial performance to 2018, are located in Part II, Item 7 - Management's Discussion and Analysis of Financial Condition and Results of Operations in our Annual Report on Form 10-K for the fiscal year ended December 31, 2019, filed with the SEC on March 2, 2020.

Overview

We are a commercial-stage biopharmaceutical company focused on changing the paradigm for the treatment of rare genetic diseases of obesity, 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, or POMC, proprotein convertase subtilisin/kexin type 1, or PCSK1, leptin receptor, or LEPR, deficiency confirmed by genetic testing. We expect IMCIVREE to be commercially available in the first quarter of 2021.

Our continued development efforts are focused on obesity related to several single gene-related, or monogenic, MC4R pathway deficiencies: Bardet-Biedl syndrome, or BBS; Alström syndrome; POMC or LEPR heterozygous deficiency obesity; steroid receptor coactivator 1, or SRC1, deficiency obesity; SH2B adapter protein 1, or SH2B1, deficiency obesity; MC4R deficiency obesity and Smith-Magenis syndrome, as well as additional disorders as part of investigator-initiated protocols. There are currently no effective or approved treatments for these MC4R pathway-related disorders. We believe that the MC4R pathway is a compelling target for treating these genetic disorders because of its critical role in regulating appetite and weight by promoting satiety and weight control, and that peptide therapeutics are uniquely suited for activating this target.

We recently 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 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. We are continuing to analyze the full data from patients with BBS or Alström syndrome, which we plan to present at a medical meeting in the first half of 2021. We plan to complete regulatory submissions to both the FDA and the EMA for BBS in the second half of 2021, and we expect to determine next steps for Alström syndrome upon completing a full analysis of the final data from the Phase 3 trial.

The U.S. Food and Drug Administration, or the FDA, has acknowledged the importance of these results by giving setmelanotide Breakthrough Therapy designation for the treatment of obesity associated with genetic defects upstream of the MC4R in the leptin melanocortin pathways. The Breakthrough Therapy designation currently covers indications for POMC deficiency obesity, LEPR deficiency obesity, BBS and Alström syndrome.

We have ongoing Phase 2 clinical trials, referred to as our Basket Study, in MC4R pathway heterozygous deficiency obesity and POMC epigenetic disorders, which we expanded in the second half of 2019 to include the following additional indications: SRC1 deficiency obesity, SH2B1 deficiency obesity, MC4R deficiency obesity and Smith-Magenis syndrome. We reported preliminary results in MC4R pathway heterozygous deficiency obesity in March 2019. 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. 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. Consistent with prior clinical experience, setmelanotide was generally well tolerated in each of these rare genetic diseases of obesity. 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.

We recently 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.

In the first half of 2021, we plan to initiate a Phase 2 clinical trial in hypothalamic obesity, initiate a potentially registration-enabling 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. Also in the second half of 2021, we expect to obtain regulatory approval from the European Commission and make IMCIVREE commercially available in Europe in obesities due to POMC, PCSK1 and LEPR deficiencies.

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 PRV Transfer closed on February 17, 2021.

On February 9, 2021, we completed an underwritten public offering in which we sold 5,750,000 shares of our common stock at a public offering price of $30.00 per share, which included the exercise in full by the underwriters of their option to purchase up to 750,000 additional shares of common stock. We received aggregate net proceeds from the offering of approximately $161.6 million after deducting underwriting discounts and commissions and offering expenses payable by us.

Our operations to date have been limited primarily to conducting research and development activities for setmelanotide. To date, we have not generated any product revenue and have financed our operations primarily through the proceeds received from the sales of common and preferred stock, asset sales, as well as capital contributions from the former parent company, Rhythm Holdings LLC. From August 2015 through August 2017, we raised aggregate net proceeds of $80.8 million through our issuance of series A preferred stock. Since our initial public offering, or IPO, on October 10, 2017 and our underwritten follow-on offerings through February 2021, we have raised aggregate net proceeds of approximately $611.4 million through the issuance of our common stock after deducting underwriting discounts, commissions and offering related transaction costs. Since inception, we have received a further $100.0 million from asset sales, specifically in connection with the PRV Transfer. We will not generate revenue from product sales until we are able to successfully establish a marketing and commercialization infrastructure for IMCIVREE. We expect to make IMCIVREE commercially available to patients 6 years of age and older with obesity due to POMC, PCSK1 or LEPR deficiency in the U.S. in the first quarter of 2021. We expect to continue to fund our operations through the sale of equity, debt financings or other sources. We intend to build our own marketing and commercial sales infrastructure and we may enter into collaborations with other parties for certain markets outside the United States. However, we may be unable to raise additional funds or enter into such other arrangements when needed on favorable terms, or at all. If we fail to raise capital or enter into such other arrangements as, and when, needed, we may have to significantly delay, scale back or discontinue the development or commercialization of setmelanotide.

As of December 31, 2020 we had an accumulated deficit of $459.3 million. Our net losses were $134.0 million and $140.7 million, for the years ended December 31, 2020 and 2019, respectively. We expect to continue to incur significant expenses and increasing operating losses over the foreseeable future. We expect our expenses will increase substantially in connection with our ongoing activities, as we:

- continue to conduct clinical trials for setmelanotide;

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

As of December 31, 2020, our cash and cash equivalents and short-term investments were approximately $172.8 million. We expect that our cash and cash equivalents and short-term investments as of December 31, 2020, together with the aggregate net proceeds from the February 2021 public offering and the proceeds from the PRV Transfer of approximately $260.1 million, will enable us to fund our operating expenses through at least the second half of 2023.

Corporate Background

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.

Impact of Novel Coronavirus

We are closely monitoring how the spread of COVID-19 is affecting our employees, business, preclinical studies and clinical trials. In response to the COVID-19 pandemic, we have limited access to our executive offices with most employees continuing their work outside of our offices and travel has been restricted. We have recently updated our timelines on the Basket Study but the changes were unrelated to COVID-19. We are continuing our regular interactions with the FDA and EMA and based on current information. We do not currently anticipate any disruption in the clinical supply of setmelanotide and our CMOs have indicated that they have appropriate plans and procedures in place to ensure uninterrupted future supply of clinical and commercial-grade setmelanotide, subject to potential limitations on their operations due to COVID-19. As a result, we do not currently expect that the COVID-19 pandemic will have a material impact on our business, results of operations and financial condition. At this time, however, there is still uncertainty relating to the trajectory of the pandemic and the impact of related responses, and disruptions caused by the COVID-19 pandemic have resulted and may in the future result in difficulties or delays in initiating, enrolling, conducting or completing our planned and ongoing clinical trials and the incurrence of unforeseen costs as a result of disruptions in clinical supply or preclinical study or clinical trial delays. For example, we experienced interruption of key clinical trial activities, such as patient attendance and clinical trial site monitoring, in our Phase 3 clinical trial evaluating setmelanotide for the treatment of insatiable hunger and severe obesity in individuals with BBS or Alström syndrome. The impact of COVID-19 on our future results will largely depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as the ultimate geographic spread of the disease, the duration of the pandemic, travel restrictions and social distancing in the United States and other countries, business closures or business disruptions, the ultimate impact on financial markets and the global economy, the effectiveness of vaccines and vaccine distribution efforts and the effectiveness of other actions taken in the United States and other countries to contain and treat the disease. See "Risk Factors—The COVID-19 pandemic has and may continue to adversely impact our business, including our preclinical studies, clinical trials and our commercialization prospects." in Part I, Item 1A of this Annual Report.

Financial Operations Overview

Revenue

To date, we have not generated any revenue from product sales. Our lead product candidate, IMCIVREE, was recently approved by the FDA for chronic weight management in adult and pediatric patients six years of age and older with obesity due to POMC, PCSK1 or LEPR deficiency confirmed by genetic testing. We expect IMCIVREE to be commercially available in the first quarter of 2021. We cannot predict if, when, or to what extent we will generate revenues from the commercialization and sale of IMCIVREE.

Research and development expenses

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

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

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

The following table summarizes our current research and development expenses:

	Year ended December 31,	
Research and development summary	**2020**	**2019**
Research and development expense	$ 90,450	$ 109,450

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

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

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

Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect research and development costs to

increase significantly for the foreseeable future as our setmelanotide and other development programs progress. However, we do not believe that it is possible at this time to accurately project total program-specific expenses to commercialization and there can be no guarantee that we can meet the funding needs associated with these expenses.

Selling, general and administrative expenses

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

General and administrative expenses consist primarily of salaries and other related costs, including stock-based compensation, relating to our full-time employees not involved in R&D or commercial activities. Other significant costs include rent, legal fees relating to patent and corporate matters and fees for accounting and consulting services.

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

	Year ended December 31,	
Selling, general and administrative summary	**2020**	**2019**
Selling, general and administrative expense	$ 46,125	$ 36,550

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

Critical Accounting Policies and Estimates

Our management's discussion and analysis of our financial condition and results of operations are based on our financial statements, which we have prepared in accordance with accounting principles generally accepted in the United States, or GAAP. The preparation of these financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements, as well as the reported amounts of revenues and expenses during the reporting periods. These items are monitored and analyzed by us for changes in facts and circumstances on an ongoing basis, and material changes in these estimates could occur in the future. We base our estimates on historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

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

Accrued research and development expenses

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

statements based on facts and circumstances known to us at the time those financial statements are prepared. We periodically confirm the accuracy of our estimates with the service providers and make adjustments if necessary. The significant estimates in our accrued research and development expenses include fees paid to CROs, CMOs and consultants in connection with research and development activities.

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

Stock-based compensation

We have a 2017 equity incentive plan, or the 2017 Plan. The 2017 Plan provides for the grant of incentive and non-qualified stock options and restricted stock and stock grants to employees, consultants, advisors and directors, as determined by the Board of Directors. As of December 31, 2020, we had reserved 7,484,536 shares of common stock under the 2017 Plan. Shares of common stock issued pursuant to awards are generally issued from authorized but unissued shares. The 2017 Plan provides that the exercise price of incentive stock options cannot be less than 100% of the fair market value of the common stock on the date of the award for participants who own less than 10% of the total combined voting power of stock, and not less than 110% for participants who own more than 10% of the voting power. Awards granted under the 2017 Plan will vest over periods as determined by our Compensation Committee and approved by our Board of Directors.

We estimate the fair value of our stock option awards to employees and non-employees using the Black-Scholes option-pricing model, which requires the input of subjective assumptions, including (a) the expected volatility of our stock, (b) the expected term of the award, (c) the risk-free interest rate, and (d) expected dividends. Previously due to the lack of a public market for the trading of our common stock and a lack of company-specific historical and implied volatility data, we based our estimate of expected volatility on the historical volatility of a group of companies in the pharmaceutical and biotechnology industries in a similar stage of development as us and that are publicly traded. For these analyses, we selected companies with comparable characteristics to ours including enterprise value, risk profiles and with historical share price information sufficient to meet the expected life of the stock-based awards. We compute the historical volatility data using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of our stock-based awards. During 2020, we began to estimate volatility by using a blend of our stock price history for the length of time we have market data for our stock and the historical volatility of similar public companies for the expected term of each grant. We will continue to apply this process until a sufficient amount of historical information regarding the volatility of our own stock price becomes available.

We have estimated the expected life of our employee stock options using the "simplified" method, whereby, the expected life equals the average of the vesting term and the original contractual term of the option. The risk-free interest rates for periods within the expected life of the option are based on the U.S. Treasury yield curve in effect during the period the options were granted. We have elected to account for forfeitures as they occur. Upon adopting Accounting Standards Update 2018-07, *Improvements to Nonemployee Share-Based Payment Accounting (Topic 718)* on July 1, 2018, we elected that unsettled equity-classified awards to nonemployees for which a measurement date has not been established be measured using the adoption date fair value.

Income taxes

We account for uncertain tax positions in accordance with the provisions of Accounting Standards Codification, or ASC, Topic 740, *Accounting for Income Taxes*, or ASC 740. When uncertain tax positions exist, we recognize the tax benefit of tax positions to the extent that the benefit will more likely than not be realized. The determination as to whether the tax benefit will more likely than not be realized is based upon the technical merits of the tax position as well as consideration of the available facts and circumstances. As of December 31, 2020, we did not have any uncertain tax positions.

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

As of December 31, 2020, we had net operating loss carryforwards to reduce federal and state incomes taxes of approximately $382.3 million and $351.2 million, respectively. If not utilized, these carryforwards begin to expire in 2033. Of the federal net operating loss carryforwards at December 31, 2020, $309.1 million can be carried forward indefinitely. At December 31, 2020, we also had available research and development tax credits for federal and state income tax purposes of approximately $8.1 million and $2.8 million, respectively. Additionally, as of December 31, 2020, we had federal orphan drug credits related to qualifying research of $10.1 million. These tax credit carryforwards begin to expire in 2033 for federal purposes and 2028 for state purposes.

Utilization of the net operating loss and tax credit carryforwards may be subject to a substantial annual limitation due to ownership change limitations that have occurred previously or that could occur in the future, as provided by Section 382 of the Internal Revenue Code of 1986, as amended, or the Code, or Section 382, as well as similar state provisions and other provisions of the Code. Ownership changes may limit the amount of net operating losses and tax credit carryforwards that can be utilized annually to offset future taxable income and tax, respectively. In general, an ownership change, as defined by Section 382, results from transactions that increase the ownership of 5.0% stockholders in the stock of a corporation by more than 50% in the aggregate over a three-year period.

Results of Operations

Comparison of years ended December 31, 2020 and 2019.

The following table summarizes our results of operations for the years ended December 31, 2020 and 2019, together with the changes in those items in dollars and as a percentage:

	Year Ended December 31,		Change	
	2020	2019	$	%
	(in thousands)			
Statement of Operations Data:				
Operating Expenses:				
Research and development	$ 90,450	$ 109,450	$ (19,000)	(17)%
Selling, general, and administrative	46,125	36,550	9,575	26 %
Total operating expenses	136,575	146,000	(9,425)	(6)%
Loss from operations	(136,575)	(146,000)	9,425	(6)%
Other income, net	2,579	5,271	(2,692)	(51)%
Net loss	$ (133,996)	$ (140,729)	$ 6,733	(5)%

Research and development expense. Research and development expense decreased by $19.0 million to $90.5 million in 2020 from $109.5 million in 2019, a decrease of 17%. The decrease was primarily due to the following:

- a decrease of $15.7 million related to our clinical trials associated with setmelanotide. We completed the GO-ID genotyping study, the POMC and LEPR Phase 3 studies and the once weekly formulation study in early to mid-2020. These decreases were slightly offset by increases related to the expansion of the Phase 2 basket study as well as starting a new renal insufficiency PK study in 2020;

- a decrease of $8.7 million related to translational research and genetic sequencing efforts, as the completion of the GO-ID study resulted in lower sequencing volume; and

- a decrease of $2.4 million related to fewer travel related expenses and conference related programs due to the Covid-19 restrictions in place for most of 2020.

The above decreases were partially offset by:

- an increase of $2.4 million due to the hiring of additional full-time employees in order to support the growth of our research and development programs, as well as efforts to support our education programs for physicians, care providers and patients who are facing rare genetic disorders of obesity;

- an increase of $2.5 million primarily related to purchases of setmelanotide API and drug product for clinical trials and preparation for potential commercialization; and

- an increase of $3.0 million due to the milestone expenses associated with the license agreement with Ipsen on filing the NDA and MMA for setmelanotide for the treatment of POMC and LEPR deficiency obesities.

Selling, general and administrative expense. Selling, general and administrative expense increased by $9.6 million to $46.1 million in 2020 from $36.6 million in 2019, an increase of 26%. The increase was primarily due to the following:

- an increase of approximately $0.9 million in cash related charges incurred with the separation agreements with our former CEO and CCO, and $4.9 million in non-cash related stock compensation expenses related with those separation agreements as well as the hiring of our current CEO in July 2020; and an increase of

approximately $0.5 million for employee related costs in connection with the hiring of additional full-time employees to support planned commercial and operating activities;

- an increase of $1.7 million related to efforts to drive patient engagement and disease awareness about rare genetic causes of obesity and prepare for the potential commercialization of setmelanotide in the U.S.; and

- an increase of $1.2 million related to consulting activity for market access development, legal services and other costs associated with activities and implementation of certain processes relating to our compliance with the Sarbanes Oxley Act.

Liquidity and Capital Resources

As of December 31, 2020, our cash and cash equivalents and short-term investments were approximately $172.8 million.

Cash flows

The following table provides information regarding our cash flows for the years ended December 31, 2020 and 2019:

	Year Ended December 31,	
	2020	2019
	(in thousands)	
Net cash provided by (used in):		
Operating activities	$ (121,980)	$ (122,750)
Investing activities	158,531	(27,970)
Financing activities	2,009	163,474
Net increase in cash, cash equivalents and restricted cash	$ 38,560	12,754

Net cash used in operating activities

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

Net cash used in operating activities was $122.0 million for the year ended December 31, 2020, and consisted primarily of a net loss of $116.1 million adjusted for non-cash items, which consisted of non-cash stock-based compensation, depreciation and amortization and rent expense. The change in operating assets and liabilities reflected a total use of cash of approximately $5.9 million for a decrease in prepaid assets, accounts payable and accrued expenses due to the timing of payments and a reduction of overall operating expenses.

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

Net cash provided by (used in) investing activities

Net cash provided by investing activities for the year ended December 31, 2020 relates to the net maturities of short-term investments of $158.7 million.

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

Net cash provided by financing activities

Net cash provided by financing activities was $2.0 million for the year ended December 31, 2020, which represents cash proceeds from the exercise of stock options and the issuance of common stock from the ESPP.

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

Funding requirements

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

We expect that our cash and cash equivalents and short-term investments as of December 31, 2020, together with the proceeds from the sale of the PRV Transfer and the net proceeds from the 2021 February public offering of approximately $260.1 million, will enable us to fund our operating expenses through at least the second half of 2023. We may need to obtain substantial additional funding in connection with our research and development activities and any continuing operations thereafter. If we are unable to raise capital when needed or on favorable terms, we would be forced to delay, reduce or eliminate our research and development programs or future commercialization efforts.

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

- the costs to commercialize setmelanotide, by building an internal sales force or entering into collaborations with third parties and providing support services for patients;
- the scope, progress, results and costs of clinical trials for our setmelanotide program;
- the costs, timing and outcome of regulatory review of our setmelanotide program;
- the obligations owed to Ipsen Pharma S.A.S., or Ipsen, Camurus AB, or Camurus and Takeda pursuant to our license agreements;
- the extent to which we acquire or in-license other product candidates and technologies;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- our ability to establish and maintain additional collaborations on favorable terms, if at all; and
- the costs of operating as a public company and losing our emerging growth company status.

Although IMCIVREE has been approved by the FDA in certain indications, and we expect IMCIVREE to be commercially available in the first quarter of 2021, IMCIVREE may not achieve commercial success. In addition, developing our setmelanotide program is a time-consuming, expensive and uncertain process that may take years to complete, and we may never generate the necessary data or results required to obtain future marketing approvals and

achieve product sales. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all.

In addition, the magnitude and duration of the COVID-19 pandemic and its impact on our liquidity and future funding requirements is uncertain as of the filing date of this Annual Report as this continues to evolve globally. See "Impact of Novel Coronavirus" above and "Risk Factors— The COVID-19 pandemic has and may continue to adversely impact our business, including our preclinical studies, clinical trials and our commercialization prospects." in Part I, Item 1A of this Annual Report for a further discussion of the possible impact of the COVID-19 pandemic on our business.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and licensing arrangements.

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

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

Contractual obligations

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

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

Based on our current development plans as of December 31, 2020, potential payments due to third parties, during the next 12 months from the filing of this Annual Report are estimated to be approximately $9.0 million in commercial milestones, in connection with our license agreements. These milestones generally become due and payable upon achievement of such milestones or sales. When the achievement of these milestones or

sales have not occurred, such contingencies are not recorded in our financial statements and are excluded from the table below.

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

Recent Accounting Pronouncements

For a discussion of pending and recently adopted accounting pronouncements, see Note 2 to our audited consolidated financial statements included elsewhere in this Annual Report.

Off-Balance Sheet Arrangements

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

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

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

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

Item 8. Financial Statements and Supplementary Data

See the consolidated financial statements filed as part of this Annual Report as listed under Item 15 below.

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

Not Applicable.

Item 9A. Controls and Procedures

Limitations on Effectiveness of Controls and Procedures

In designing and evaluating our disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives. In addition, the design of disclosure controls and procedures must reflect the fact that there are resource constraints and that management is required to apply judgment in evaluating the benefits of possible controls and procedures relative to their costs.

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our principal executive officer and principal financial officer, has evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13a- 15(e) and 15d- 15(e) under the Securities Exchange Act of 1934, as amended, as of the end of the period covered by this Annual Report. Based on such evaluation, our principal executive officer and principal financial officer have concluded that as of December 31, 2020, our disclosure controls and procedures were effective at the reasonable assurance level.

Management's Annual Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act).

Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2020. In making this assessment, it used the criteria established in *Internal Control—Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). Based on such assessment, our management has concluded that our internal control over financial reporting was effective, as of December 31, 2020. Ernst & Young LLP, our independent registered public accounting firm, has issued an attestation report on our internal control over financial reporting, which appears in this Item under the heading "Report of Independent Registered Public Accounting Firm" below.

Changes in Internal Control Over Financial Reporting

There were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) that occurred during the fourth quarter of 2020 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Stockholders and the Board of Directors of Rhythm Pharmaceuticals, Inc.

Opinion on Internal Control Over Financial Reporting

We have audited Rhythm Pharmaceuticals, Inc.'s internal control over financial reporting as of December 31, 2020, based on criteria established in Internal Control – Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework), (the COSO criteria). In our opinion, Rhythm Pharmaceuticals, Inc. (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2020, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2020 and 2019, the related consolidated statements of operations and comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2020, and the related notes and our report dated March 1, 2021 expressed an unqualified opinion thereon.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Annual Report on Internal Control over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects.

Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control Over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ Ernst & Young LLP

Boston, Massachusetts
March 1, 2021

Item 9B. Other Information

None

PART III

Item 10. Directors, Executive Officers and Corporate Governance

We have adopted a Code of Business Conduct and Ethics for all of our directors, officers and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. We have posted a current copy of our Code of Business Conduct and Ethics on our website at *www.rhythmtx.com* in the "Investors & Media" section under "Corporate Governance." We intend to disclose on our website any amendments to, or waivers from, our Code of Business Conduct and Ethics that are required to be disclosed pursuant to the rules of the SEC, as well as Nasdaq's requirement to disclose waivers with respect to directors and executive officers. The information contained on our website is not considered part of, or incorporated by reference into, this Annual Report or any other filing that we make with the SEC.

The remaining information required under this item is incorporated herein by reference to our definitive proxy statement for our 2021 annual meeting of stockholders, which proxy statement will be filed with the Securities and Exchange Commission not later than 120 days after the close of our fiscal year ended December 31, 2020.

Item 11. Executive Compensation

The information required under this item is incorporated herein by reference to our definitive proxy statement for our 2021 annual meeting of stockholders, which proxy statement will be filed with the Securities and Exchange commission not later than 120 days after the close of our fiscal year ended December 31, 2020.

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

Equity Compensation Plan Information

The following table provides information as of December 31, 2020, regarding our common stock that may be issued under (1) our 2017 Equity Incentive Plan, or the 2017 Plan; and (2) our 2017 Employee Stock Purchase Plan, or the 2017 ESPP.

Plan Category:	Number of Securities to be Issued Upon Exercise of Outstanding Options, Warrants and Rights	Weighted-Average Exercise Price of Outstanding Options, Warrants and Rights	Number of Securities Available for Future Issuance Under Equity Compensation Plans
Equity compensation plans approved by stockholders			
2017 Plan	5,375,772	$ 21.30	2,108,764
2017 ESPP	—	—	1,000,993
Equity compensation plans not approved by stockholders	—	—	—
Total	5,375,772	$ 21.30	3,109,757

(1) The 2017 Plan provides for an annual increase on each January 1 commencing on January 1, 2018, by an amount equal to 4% of the number of shares of common stock outstanding as of the end of the immediately preceding fiscal year, provided that the Board may provide for no increase or that the increase will be a lesser number of shares.

(2) The 2017 ESPP provides for an annual increase on each January 1 commencing on January 1, 2018 and ending on and including January 1, 2027, by an amount equal to the lesser of (i) 1% of the number of shares of common stock outstanding as of the end of the immediately preceding fiscal year or (ii) 682,102, provided that the Board may provide for no increase or that the increase will be a lesser number of shares.

Other

The remaining information required under this item is incorporated herein by reference to our definitive proxy statement for our 2021 annual meeting of stockholders, which proxy statement will be filed with the Securities and Exchange commission not later than 120 days after the close of our fiscal year ended December 31, 2020.

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

The information required under this item is incorporated herein by reference to our definitive proxy statement for our 2021 annual meeting of stockholders, which proxy statement will be filed with the Securities and Exchange commission not later than 120 days after the close of our fiscal year ended December 31, 2020.

Item 14. Principal Accountant Fees and Services

The information required under this item is incorporated herein by reference to our definitive proxy statement for our 2021 annual meeting of stockholders, which proxy statement will be filed with the Securities and Exchange commission not later than 120 days after the close of our fiscal year ended December 31, 2020.

PART IV

Item 15. Exhibits and Financial Statement Schedules

(a) 1. Consolidated Financial Statements.

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

2. Financial Statement Schedules.

All financial statement schedules have been omitted because the required information is either presented in the consolidated financial statements or the notes thereto or is not applicable or required.

3. List of Exhibits.

The following is a list of exhibits filed as part of this Annual Report.

Exhibit Index

Exhibit Number	Exhibit Description	Incorporated by Reference		
		Form	Date	Number
2.1	Asset Purchase Agreement, dated January 5, 2021, between the Registrant and Alexion Pharmaceuticals, Inc.	8-K	1/5/2021	2.1
3.1	Amended and Restated Certificate of Incorporation.	10-Q	5/4/2020	3.1
3.2	Amended and Restated Bylaws.	8-K	12/11/2020	3.1
4.1	Form of Common Stock Certificate.	S-1/A	9/25/2017	4.1
4.2	Amended and Restated Investors' Rights Agreement, dated August 21, 2017.	S-1	9/5/2017	4.2
4.3	Form of Subordinated Indenture to be entered into between the Registrant and a trustee acceptable to the registrant.	S-3	11/9/2018	4.3
4.4	Form of Senior Indenture to be entered into between the Registrant and a trustee acceptable to the registrant.	S-3	11/9/2018	4.4
4.5	Description of the Registrant's Securities registered pursuant to Section 12 of the Securities Exchange Act of 1934.	10-K	3/2/2020	4.5
10.1†	Form of Indemnification Agreement.	S-1/A	9/25/2017	10.1
10.2†	2015 Equity Incentive Plan and Form of Option Agreement and Notice of Exercise.	S-1/A	9/25/2017	10.21
10.3.1†	2017 Equity Incentive Plan and Form of Option Agreement and Notice of Exercise.	10-Q	11/14/2017	10.2
10.3.2†	2017 Equity Incentive Plan Restricted Stock Unit Award Agreement	10-K	3/2/2020	10.18
10.4.1†	2017 Employee Stock Purchase Plan	10-Q	11/14/2017	10.10
10.4.2†	First Amendment to the 2017 Employee Stock Purchase Plan	S-1	6/18/2018	10.17
10.5†*	Summary of Non-Employee Director Compensation Policy			
10.6‡	License Agreement, dated March 21, 2013, by and between the Registrant (f/k/a Rhythm Metabolic, Inc.) and Ipsen Pharma S.A.S.	S-1	9/5/2017	10.6
10.7‡	License Agreement, dated January 4, 2016, by and between the Registrant and Camurus AB.	S-1	9/5/2017	10.8
10.8‡	License Agreement, dated March 30, 2018, by and between the Registrant and Takeda Pharmaceutical Company Limited.	10-Q	5/14/2018	10.1
10.9.1‡	Development and Manufacturing Services Agreement, dated July 17, 2013, by and between the Registrant (f/k/a Rhythm Metabolic, Inc.) and Peptisyntha Inc. (n/k/a Corden Pharma International).	S-1	9/5/2017	10.7
10.9.2‡	First Amendment to Development and Manufacturing Services Agreement, dated February 20, 2020, by and between the Registrant and Corden Pharma Brussels S.A.	10-Q	5/4/2020	10.3
10.9.3‡	Second Amendment to Development and Manufacturing Services Agreement, dated July	10-Q	8/3/2020	10.1

	15, 2020, by and between the Registrant and Corden Pharma Brussels S.A.			
10.10	Development and Manufacturing Services Agreement, dated as of December 21, 2016, by and between Registrant and Recipharm Monts S.A.S.	S-1	9/5/2017	10.15
10.11.1	Lease, dated November 25, 2015, by and between the Registrant and 500 Boylston & 222 Berkeley Owner (DE) LLC.	S-1	9/5/2017	10.11
10.11.2	First Amendment to Lease, dated April 15, 2016, by and between the Registrant and 500 Boylston & 222 Berkeley Owner (DE) LLC.	10-K	3/8/2019	10.9
10.11.3	Second Amendment to Lease, dated August 6, 2018, by and between the Registrant and 500 Boylston & 222 Berkeley Owner (DE) LLC.	8-K	8/9/2018	10.1
10.12†	Offer Letter, dated December 21, 2017, by and between the Registrant and Hunter Smith.	10-Q	5/4/2020	10.2
10.13†	Offer Letter, dated September 4, 2020, by and between the Registrant and Yann Mazabraud.	10-Q	11/2/2020	10.1
10.14†*	Offer Letter, dated May 10, 2018, by and between the Registrant and Simon D. Kelner.			
10.15†*	Offer Letter, dated September 14, 2018, by and between the Registrant and Murray Stewart M.D.			
10.16†*	Offer Letter, dated September 25, 2020, by and between the Registrant and Jennifer Chien.			
10.17†	Offer Letter, dated July 16, 2020, by and between the Registrant and David P. Meeker M.D.	8-K	7/21/2020	10.1
10.18.1†	Offer Letter, dated September 13, 2017, by and between the Registrant and Keith M. Gottesdiener	10-Q	8/8/2018	10.2
10.18.2†	Separation Agreement and General Release, by and between the Registrant and Keith Gottesdiener, dated January 6, 2020.	8-K	1/8/2020	10.1
10.18.3†	Consulting Agreement, by and between the Registrant and Keith Gottesdiener, dated January 6, 2020.	8-K	1/8/2020	10.2
10.19.1†	Offer Letter, dated September 13, 2017, by and between the Registrant and Nithya Desikan	10-Q	8/8/2018	10.4
10.19.2†	Separation Agreement, dated September 30, 2020, by and between the Registrant and Nithya Desikan.	10-Q	11/2/2020	10.2
21.1*	List of Subsidiaries.			
23.1*	Consent of Ernst & Young LLP, Independent Registered Public Accounting Firm.			
31.1*	Certification of the Chief Executive Officer, as required by Section 302 of the Sarbanes-Oxley Act of 2002 (18 U.S.C. 1350).			
31.2*	Certification of the Chief Financial Officer, as required by Section 302 of the Sarbanes-Oxley Act of 2002 (18 U.S.C. 1350).			
32.1**	Certification of the Chief Executive Officer, as required by Section 906 of the Sarbanes-Oxley Act of 2002 (18 U.S.C. 1350).			

32.2**	Certification of the Chief Financial Officer, as required by Section 906 of the Sarbanes-Oxley Act of 2002 (18 U.S.C. 1350).
101.INS*	Inline XBRL Instance Document- the Instance Document does not appear in the interactive data file because its XBRL tags are embedded within the Inline XBRL document.
101.SCH*	Inline XBRL Taxonomy Extension Schema Document.
101.CAL*	Inline XBRL Taxonomy Extension Calculation Linkbase Document.
101.DEF*	Inline XBRL Taxonomy Extension Definition Linkbase Document.
101.LAB*	Inline XBRL Taxonomy Extension Label Linkbase Document.
101.PRE*	Inline XBRL Taxonomy Extension Presentation Linkbase Document.
104	Cover Page Interactive Data File (formatted as Inline XBRL and contained in Exhibit 101).

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

Item 16. Form 10-K Summary

None

SIGNATURES

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

RHYTHM PHARMACEUTICALS, INC.

By: /s/ David P. Meeker M.D.
David P. Meeker M.D.
President and Chief Executive Officer

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

Name	Title	Date
/s/ David P. Meeker M.D. David P. Meeker M.D.	Chief Executive Officer, Director, Chairman of the Board (Principal Executive Officer)	March 1, 2021
/s/ Hunter Smith Hunter Smith	Chief Financial Officer (Principal Financial and Accounting Officer)	March 1, 2021
/s/ Edward T. Mathers Edward T. Mathers	Lead Director	March 1, 2021
/s/ Stuart Arbuckle Stuart Arbuckle	Director	March 1, 2021
/s/ Camille L. Bedrosian, M.D. Camille L. Bedrosian M.D.	Director	March 1, 2021
/s/ Todd Foley Todd Foley	Director	March 1, 2021
/s/ Jennifer L. Good Jennifer L. Good	Director	March 1, 2021
/s/ Christophe R. Jean Christophe R. Jean	Director	March 1, 2021
/s/ David W. J. McGirr David W. J. McGirr	Director	March 1, 2021
/s/ Lynn A. Tetrault Lynn A. Tetrault	Director	March 1, 2021

RHYTHM PHARMACEUTICALS, INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Stockholders and the Board of Directors of Rhythm Pharmaceuticals, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Rhythm Pharmaceuticals, Inc. (the Company) as of December 31, 2020 and 2019, the related consolidated statements of operations and comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2020, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2020 and 2019, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2020, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2020, based on criteria established in Internal Control – Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework), and our report dated March 1, 2021 expressed an unqualified opinion thereon.

Adoption of New Accounting Standards

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

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current period audit of the financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of the critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Accrued and Prepaid Research and Development Expenses

Description of the Matter

The Company's total accrued expenses and other current liabilities were $12.6 million at December 31, 2020, which included the estimated obligation for research and development expenses incurred as of December 31, 2020 but not paid as of that date. In addition, the Company's total prepaid expenses and other current assets were $8.9 million at December 31, 2020, which included amounts that were paid in advance of services incurred pursuant to research and development activities. As discussed in Note 2 of the consolidated financial statements, the Company's research and development expenses are based on the Company's estimates of the progress of the related studies or clinical trials, including the phase or completion of events, invoices received, and contracted costs, which results in an accrual or prepayment at period end.

How We Addressed the Matter in Our Audit

Auditing the Company's accrued and prepaid research and development expenses was especially challenging due to the application of significant management judgment about the estimate of services provided but not yet invoiced. Specifically, the amount of accrued and prepaid research and development expenses recognized is sensitive to the availability of information to make the estimate, including the estimate of the period over which services will be performed, the associated cost of such services, and the level of services performed and progress in the period for which the Company has not yet received an invoice from the supplier. Additionally, due to the long duration of clinical trials and the timing of invoicing received from third parties, the actual amounts incurred are not always known by the report date.

To evaluate the Company's estimate of services incurred as of period end pursuant to its research and development activities, our audit procedures included, among others, testing the completeness and accuracy of the underlying data used in the estimates and evaluating the significant assumptions stated above that are used by management to estimate the recorded amounts. To assess the reasonableness of the significant assumptions, we obtained information regarding the nature and extent of progress of clinical trials and other activities from the Company's research and development personnel that oversee the clinical trials and obtained information directly from third parties which indicated the third parties' estimate of costs incurred to date. To evaluate the completeness and valuation of the accrued or prepaid research and development expenses, we compared invoices received by the Company subsequent to December 31, 2020 to the amounts recognized by the Company as of that date. We inspected the Company's contracts with third parties and any pending change orders to assess the impact to the amounts recorded. We also independently estimated the services incurred by the respective third-party and compared it to the amount recognized by the Company.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2015.
Boston, Massachusetts
March 1, 2021

RHYTHM PHARMACEUTICALS, INC.

CONSOLIDATED BALANCE SHEETS

(in thousands, except share and per share data)

	December 31, 2020	December 31, 2019
Assets		
Current assets:		
Cash and cash equivalents	$ 100,854	$ 62,294
Short-term investments	71,938	230,165
Prepaid expenses and other current assets	8,876	9,945
Total current assets	181,668	302,404
Property and equipment, net	3,195	3,671
Right-of-use asset	1,807	2,045
Restricted cash	403	403
Total assets	$ 187,073	$ 308,523
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 4,900	$ 10,415
Accrued expenses and other current liabilities	12,559	13,530
Lease liability	535	472
Total current liabilities	17,994	24,417
Long-term liabilities:		
Lease liability	2,551	3,086
Total liabilities	20,545	27,503
Commitments and contingencies (Notes 5 and 9)		
Stockholders' equity:		
Preferred Stock, $0.001 par value: 10,000,000 shares authorized; no shares issued and outstanding at December 31, 2020 and December 31, 2019	—	—
Common stock, $0.001 par value: 120,000,000 shares authorized; 44,235,903 and 43,996,753 shares issued and outstanding at December 31, 2020 and December 31, 2019, respectively	44	44
Additional paid-in capital	625,762	606,307
Accumulated other comprehensive income	49	—
Accumulated deficit	(459,327)	(325,331)
Total stockholders' equity	166,528	281,020
Total liabilities and stockholders' equity	$ 187,073	$ 308,523

The accompanying notes are an integral part of these financial statements

RHYTHM PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS

(in thousands, except share and per share data)

	Year Ended December 31, 2020	Year Ended December 31, 2019	Year Ended December 31, 2018
Operating expenses:			
Research and development	$ 90,450	$ 109,450	$ 50,337
Selling, general, and administrative	46,125	36,550	28,080
Total operating expenses	136,575	146,000	78,417
Loss from operations	(136,575)	(146,000)	(78,417)
Other income (expense):			
Interest income, net	2,579	5,271	4,353
Total other income, net	2,579	5,271	4,353
Net loss	$ (133,996)	$ (140,729)	$ (74,064)
Net loss per share, basic and diluted	$ (3.04)	$ (3.86)	$ (2.39)
Weighted-average common shares outstanding, basic and diluted	44,127,220	36,422,450	31,004,047
Other comprehensive loss:			
Net loss	$ (133,996)	$ (140,729)	$ (74,064)
Unrealized gain on marketable securities	49	144	—
Comprehensive loss	$ (133,947)	$ (140,585)	$ (74,064)

The accompanying notes are an integral part of these financial statements

RHYTHM PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY

(in thousands, except share data)

	Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive Income	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balance at December 31, 2017	27,284,140	$ 27	$ 255,013	$ —	$ (110,252)	$ 144,788
Adoption of new accounting standard	—	—	286	—	(286)	—
Stock compensation expense	—	—	6,390	—	—	6,390
Shares issued for license agreement	223,544	—	4,448	—	—	4,448
Issuance of common stock upon completion of public offering, net of offering costs	6,591,800	7	162,871	—	—	162,878
Issuance of common stock in connection with exercise of stock options	311,241	—	1,808	—	—	1,808
Unrealized gain on marketable securities	—	—	8	—	—	8
Net loss	—	—	—	—	(74,064)	(74,064)
Balance at December 31, 2018	34,410,725	34	430,824	—	(184,602)	246,256
Stock compensation expense	—	—	11,875	—	—	11,875
Issuance of common stock in connection with ESPP	25,871	—	558	—	—	558
Issuance of common stock in connection with exercise of stock options	235,833	1	1,563	—	—	1,564
Issuance of common stock upon completion of public offering, net of offering costs	9,324,324	9	161,343	—	—	161,352
Unrealized gain on marketable securities	—	—	144	—	—	144
Net loss	—	—	—	—	(140,729)	(140,729)
Balance at December 31, 2019	43,996,753	44	606,307	—	(325,331)	281,020
Stock compensation expense	—	—	17,455	—	—	17,455
Issuance of common stock in connection with ESPP	30,052	—	522	—	—	522
Issuance of common stock in connection with exercise of stock options and vesting of restricted stock units	209,098	—	1,478	—	—	1,478
Unrealized gain on marketable securities	—	—	—	49	—	49
Net loss	—	—	—	—	(133,996)	(133,996)
Balance at December 31, 2020	44,235,903	$ 44	$ 625,762	$ 49	$ (459,327)	$ 166,528

The accompanying notes are an integral part of these financial statements

RHYTHM PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS

(in thousands)

	Year ended December 31,		
	2020	2019	2018
Operating activities			
Net loss	$ (133,996)	$ (140,729)	$ (74,064)
Adjustments to reconcile net loss to cash used in operating activities:			
Non-cash research and development license expense	—	—	4,448
Stock-based compensation expense	17,455	11,875	6,390
Depreciation and amortization	690	834	442
Deferred rent	(234)	203	61
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	551	(6,378)	(6,286)
Tenant improvement allowance	—	938	—
Accounts payable, accrued expenses and other current liabilities	(6,446)	10,507	6,953
Net cash used in operating activities	(121,980)	(122,750)	(62,056)
Investing activities			
Purchases of short-term investments	(86,869)	(295,825)	(248,592)
Maturities of short-term investments	245,614	271,240	162,166
Purchases of property and equipment	(214)	(3,385)	(722)
Net cash provided by (used in) investing activities	158,531	(27,970)	(87,148)
Financing activities			
Net proceeds from issuance of common stock	—	161,352	162,878
Proceeds from the exercise of stock options	1,487	1,564	1,808
Proceeds from issuance of common stock from ESPP	522	558	—
Net cash provided by financing activities	2,009	163,474	164,686
Net increase in cash, cash equivalents and restricted cash	38,560	12,754	15,482
Cash, cash equivalents and restricted cash at beginning of period	62,697	49,943	34,461
Cash, cash equivalents and restricted cash at end of period	$ 101,257	$ 62,697	$ 49,943

The accompanying notes are an integral part of these financial statements

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements

(In thousands, except share and per share information)

1. Nature of Business

Rhythm Pharmaceuticals, Inc. (the "Company" or "We"), is a commercial-stage biopharmaceutical company focused on changing the paradigm for the treatment of rare genetic diseases of obesity, 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, or POMC, proprotein convertase subtilisin/kexin type 1, or PCSK1, or leptin receptor, or LEPR, deficiency confirmed by genetic testing. We expect IMCIVREE to be commercially available in the first quarter of 2021.

The Company is a Delaware corporation organized in February 2013 under the name Rhythm Metabolic, Inc., and as of October 2015, under the name Rhythm Pharmaceuticals, Inc.

The Company's continued development efforts are focused on obesity related to several single gene-related, or monogenic, MC4R pathway deficiencies: Bardet-Biedl syndrome, or BBS; Alström syndrome; POMC or LEPR heterozygous deficiency obesity; steroid receptor coactivator 1, or SRC1, deficiency obesity; SH2B adapter protein 1, or SH2B1, deficiency obesity; MC4R deficiency obesity and Smith-Magenis syndrome, as well as additional disorders as part of investigator-initiated protocols. Currently, there are no effective or approved treatments for these MC4R pathway-related disorders. The Company believes that the MC4R pathway is a compelling target for treating these genetic disorders because of its critical role in regulating appetite and weight by promoting satiety and weight control, and that peptide therapeutics are uniquely suited for activating this target.

In March 2018, the Company acquired exclusive, worldwide rights from Takeda Pharmaceutical Company Limited ("Takeda") to develop and commercialize T-3525770 (now "RM-853"). RM-853 is a potent, orally available ghrelin o-acyltransferase ("GOAT") inhibitor currently in preclinical development for Prader-Willi Syndrome ("PWS"). PWS is a rare genetic disorder that results in hyperphagia and early-onset, life-threatening obesity, for which there are no approved therapeutic options.

The Company is subject to risks and uncertainties common to late-stage companies in the biotechnology industry, including but not limited to, risks associated with the commercialization of approved products, completing preclinical studies and clinical trials, receiving regulatory approvals for product candidates, development by competitors of new biopharmaceutical products, dependence on key personnel, protection of proprietary technology, compliance with government regulations and the ability to secure additional capital to fund operations. Commercialization of approved products will require significant resources and in order to market IMCIVREE, the Company must continue to build its sales, marketing, managerial and other non-technical capabilities or make arrangements with third parties to perform these services. Product candidates currently under development will require significant additional research and development efforts, including preclinical and clinical testing and regulatory approval, prior to commercialization. These efforts require significant amounts of additional capital, adequate personnel and infrastructure and extensive compliance-reporting capabilities. Even though the Company has an approved product, and even if the Company's further product development efforts are successful, it is uncertain when, if ever, the Company will realize revenue from product sales.

Liquidity

The Company has incurred operating losses and negative cash flows from operations since inception. As of December 31, 2020, the Company had an accumulated deficit of $459,327. The Company has primarily funded these losses through the proceeds from the sales of common and preferred stock as well as capital contributions received from the former parent company, Rhythm Holdings LLC. To date, the Company has no product revenue and management expects operating losses to continue for the foreseeable future. The Company has devoted substantially all of its resources to its drug development efforts, comprising of research and development, manufacturing, conducting clinical trials for its product candidates, protecting its intellectual property, pre-commercialization activities and general and administrative functions relating to these operations. The future success of the Company is dependent on its ability to develop its product candidates and ultimately upon its ability to attain profitable operations.

At December 31, 2020, the Company had $172,792 of cash and cash equivalents and short-term investments on hand. Subsequent to year end, the Company received additional funding in connection with the sale of a Rare Pediatric Disease Priority Review Voucher, or PRV, and a public offering (see Note 12, “Subsequent Events”). The net proceeds from the sale of the PRV Transfer and this offering, or the February 2021 public offering, were approximately $260,050 after deducting underwriting discounts and commissions and estimated offering expenses. In the future, the Company will be dependent on obtaining funding from third parties, such as proceeds from the issuance of debt, sale of equity and funded research and development programs, to maintain the Company's operations and meet the Company's obligations. There is no guarantee that additional equity or other financings will be available to the Company on acceptable terms, or at all. If the Company fails to obtain additional funding when needed, the Company would be forced to scale back, terminate its operations or seek to merge with or be acquired by another company. Management believes that the Company's existing cash resources will be sufficient to fund the Company's operations through at least the next twelve months from the filing of this Annual Report on Form 10-K with the SEC.

2. Summary of Significant Accounting Policies

Basis of Presentation

The Company's consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States (“GAAP”). Any reference in these notes to applicable guidance is meant to refer to the authoritative United States generally accepted accounting principles as found in the Accounting Standards Codification (“ASC”) and Accounting Standards Updates (“ASU”) of the Financial Accounting Standards Board (“FASB”).

Use of Estimates

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent liabilities at the date of the financial statements and the reported amounts of revenue and expenses during the reporting period. The Company bases its estimates on historical experience and other market-specific or other relevant assumptions that it believes to be reasonable under the circumstances. This process may result in actual results differing materially from those estimated amounts used in the preparation of the financial statements if these results differ from historical experience, or other assumptions do not turn out to be substantially accurate, even if such assumptions are reasonable when made. Significant estimates relied upon in preparing these financial statements include accruals related to research and development expenses, assumptions used to record stock-based compensation expense and the valuation allowance on the Company's deferred tax assets. Estimates are periodically reviewed in light of changes in circumstances, facts and experience. Changes in estimates are recorded in the period in which they become known. Actual results could differ materially from those estimates.

Principles of Consolidation

The consolidated financial statements include the accounts of Rhythm Pharmaceuticals, Inc. and its wholly-owned subsidiaries. All significant intercompany balances and transactions have been eliminated in consolidation.

Off-Balance Sheet Risk and Concentrations of Credit Risk

Financial instruments, which potentially subject the Company to significant concentration of credit risk, consist primarily of cash and cash equivalents and short-term investments, which are maintained at two federally insured financial institutions. The deposits held at these two institutions are in excess of federally insured limits. The Company has not experienced any losses in such accounts and management believes that the Company is not exposed to significant credit risk due to the financial position of the depository institutions in which those deposits are held. The Company has no off-balance sheet risk, such as foreign exchange contracts, option contracts, or other foreign hedging arrangements.

Segment Information

Operating segments are defined as components of an entity about which separate discrete information is available for evaluation by the chief operating decision maker, or decision-making group, in deciding how to allocate resources and in assessing performance. The Company considers its chief executive officer, or CEO, as its chief operating decision maker. The Company and the CEO view the Company's operations and manages its business in one operating segment operating exclusively in the United States.

Cash and Cash Equivalents

The Company considers all highly liquid investments with original or remaining maturity from the date of purchase of three months or less to be cash equivalents. Cash and cash equivalents includes bank demand deposits, U.S. treasury bills and money market funds that invest primarily in U.S. government treasuries.

Short-term Investments

Short-term investments consist of investments with original maturities greater than 90 days, as of the date of purchase. The Company has classified its investments with maturities beyond one year as short term, based on their highly liquid nature and because such marketable securities represent the investment of cash that is available for current operations. The Company considers its investment portfolio available-for-sale. Accordingly, these investments are recorded at fair value, which is based on quoted market prices. Unrealized gains and losses are reported as a component of accumulated other comprehensive income (loss) in stockholders' equity. To the extent the amortized cost basis of the available-for-sale debt securities exceeds the fair value, management assesses the debt securities for credit loss; however, management considers the risk of credit loss to be minimized by the Company's policy of investing in financial instruments issued by highly-rated financial institutions. When assessing the risk of credit loss, management considers factors such as the severity and the reason of the decline in value (i.e., any changes to the rating of the security by a rating agency or other adverse conditions specifically related to the security) and management's intended holding period and time horizon for selling. During the years ended December 31, 2020, 2019, and 2018, the Company did not recognize any credit losses related to its available-for-sale debt securities. Further, as of December 31, 2020 and 2019, the Company did not record an allowance for credit losses related to its available-for-sale debt securities.

Restricted Cash

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

Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets consist primarily of costs incurred in advance of services being received, including services related to clinical trial programs. Prepaid expenses and other current assets consists of the following:

	December 31,	
	2020	2019
Prepaid research and development costs	$ 5,828	$ 6,438
Other current assets	3,048	3,507
Prepaid expenses and other current assets	$ 8,876	$ 9,945

Property and Equipment

Property and Equipment consists of the following:

	Useful Life	December 31,	
		2020	2019
Leasehold improvements	*	$ 2,705	$ 2,705
Office equipment	5 years	70	70
Computers and software	3 years	625	411
Furniture, fixtures and equipment	5 years	1,237	1,237
		4,637	4,423
Less accumulated depreciation and amortization		(1,442)	(752)
Property and equipment, net		$ 3,195	$ 3,671

* Shorter of asset life or lease term.

Depreciation and amortization expense for the years ended December 31, 2020, 2019 and 2018 was $690, $834 and $442, respectively.

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

Fair Value Measurements

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

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

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

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

The Company's cash equivalents and marketable securities at December 31, 2020 and 2019 were carried at fair value, determined according to the fair value hierarchy. See Note 4 for further discussion.

The carrying amounts reflected in the consolidated balance sheets for accounts payable and accrued expenses approximate their fair values due to their short-term maturities at December 31, 2020 and 2019, respectively.

Government Grants

The Company obtained an Orphan Products Development grant entitled "Phase 2 study of the melanocortin 4 receptor agonist RM-493 for the treatment of Prader-Willi syndrome" in 36 patients. The grant was awarded by the Public Health Service, or PHS, Food and Drug Administration. The PHS grant is for a total of $999 and is effective July 2015 through June 2018 for reimbursement of expenses relating to the Phase 2 Prader-Willi Study.

The Company recognizes government grants upon the determination that it will comply with the conditions attached to the grant arrangement and the grant will be received. Government grants are recognized in the statements of operations on a systematic basis over the periods in which the Company recognizes the related costs for which the government grant is intended to compensate. Government grants for research and development efforts are deducted in reporting the related expense in the statement of operations. Government grant income received during the year ended December 31, 2018 of $210 is included as a deduction to research and development expense in the consolidated statements of operations and comprehensive loss. No grant income was received during the years ended December 31, 2020 or 2019.

Research and Development Expenses

Costs incurred in the research and development of the Company's products are expensed to operations as incurred. Research and development expenses consist of costs incurred in performing research and development activities, including salaries and benefits, facilities costs, overhead costs, contract services and other outside costs. The value of goods and services received from contract research organizations, or CROs, or contract manufacturing organizations, or CMOs, in the reporting period are estimated based on the level of services performed and progress in the period for which the Company has not yet received an invoice from the supplier. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the studies or clinical trials, including the phase or completion of events, invoices received and contracted costs. Significant judgments and estimates are made in determining the accrued balances at the end of any reporting period. Actual results could differ from the Company's estimates. The Company's historical accrual estimates have not been materially different from the actual costs.

Nonrefundable advance payments for goods or services to be received in the future for use in research and development activities are recorded as prepaid expenses, and expensed as the related goods are delivered or the services are performed.

Income Taxes

The Company is taxed as a C corporation for federal income tax purposes. Income taxes for the Company are recorded in accordance with FASB ASC Topic 740, *Income Taxes* ("ASC 740"), which provides for deferred taxes using an asset and liability approach. Income taxes have been calculated on a separate tax return basis.

The Company accounts for income taxes under the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the financial statements. Under this method, the Company determines deferred tax assets and liabilities on the basis of the differences between the financial statement and tax bases of assets and liabilities by using enacted tax rates in effect for the year in which the differences are expected to reverse. The effect of a change in tax rates on deferred tax assets and liabilities is recognized in income in the period that includes the enactment date. The Company recognizes deferred tax assets to the extent that it believes that these assets are more likely than not to be realized. In making such a determination, the Company considers all available positive and negative evidence, including future reversals of existing taxable temporary differences, projected future taxable income, tax-planning strategies, and results of recent operations. If the Company determines that it would be able to realize its deferred tax assets in the future in excess of their net recorded amount, it would make an adjustment to the deferred tax asset valuation allowance, which would reduce the provision for income taxes.

The Company records uncertain tax positions in accordance with ASC 740 on the basis of a two-step process in which (1) it determines whether it is more likely than not that the tax positions will be sustained on the basis of the technical merits of the position and (2) for those tax positions that meet the more-likely-than-not recognition threshold, the Company recognizes the largest amount of tax benefit that is more than 50% likely to be realized upon ultimate settlement with the related tax authority.

The Company recognizes interest and penalties related to unrecognized tax benefits on the income tax expense line in the accompanying consolidated statement of operations. As of December 31, 2020, no accrued interest or penalties are included on the related tax liability line in the consolidated balance sheet.

Net Loss Per Share

Basic net loss per share is computed by dividing net loss by the weighted average number of common shares outstanding during the period, without consideration of potential dilutive securities. Diluted net loss per share is computed by adjusting the weighted average shares outstanding for the potential dilutive effects of common stock equivalents outstanding during the period calculated in accordance with the treasury stock method. For purposes of the diluted net loss per share calculation, stock options and restricted stock units are considered to be common stock equivalents but have been excluded from the calculation of diluted net loss per share, as their effect would be anti-dilutive for all periods presented. Therefore, basic and diluted net loss per share were the same for all periods presented.

The following table includes the potential common shares, presented based on amounts outstanding at each period end, that were excluded from the computation of diluted net loss per share due to their anti-dilutive effect, for the periods indicated:

	Year Ended December 31,		
	2020	2019	2018
Stock options	5,199,235	3,428,497	2,616,530
Restricted stock units	176,537	—	—
Potential common shares	5,375,772	3,428,497	2,616,530

Comprehensive Income (Loss)

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

Patent Costs

Costs to secure and defend patents are expensed as incurred and are classified as general and administrative expenses. Patent costs were $524, $472 and $637 for the years ended December 31, 2020, 2019 and 2018, respectively.

Subsequent Events

The Company considers events or transactions that occur after the balance sheet date but prior to the issuance of the financial statements to provide additional evidence for certain estimates or to identify matters that require additional disclosure. Subsequent events have been evaluated as required.

Application of New or Revised Accounting Standards

From time to time, new accounting pronouncements are issued by the FASB and adopted by the Company as of the specified effective date. Unless otherwise discussed, the Company believes that the impact of recently issued standards that are not yet effective will not have a material impact on its financial position or results of operations upon adoption.

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

In June 2016, the FASB issued ASU 2016-13, *Financial Instruments-Credit Losses-Measurement of Credit Losses on Financial Instruments*, which has been subsequently amended by ASU No. 2018-19, ASU No. 2019-04, ASU No. 2019-05, ASU No. 2019-10, ASU No. 2019-11 and ASU No. 2020-03, or ASU 2016-13. The provisions of ASU 2016-13 modify the impairment model to utilize an expected loss methodology in place of the currently used incurred loss methodology and require a consideration of a broader range of reasonable and supportable information to inform credit loss estimates. Since the Company ceased to be an emerging growth company as of December 31, 2020, the Company adopted the standard during the fourth quarter of 2020 and applied the modified retrospective method of adoption to the Company's financial statements as of January 1, 2020. Based on the composition of the investment portfolio as of the adoption date and at December 31, 2020 , the adoption of this standard did not have a material impact on the Company's financial position, results of operations and cash flows for the year ended December 31 2020 and no adjustment was required to be recorded to the opening retained earnings balance as of January 1, 2020.

In December 2019, the FASB issued ASU 2019-12, *Income Taxes-Simplifying the Accounting for Income Taxes*, or ASU 2019-12. ASU 2019-12 eliminates certain exceptions related to the approach for intraperiod tax allocation, the methodology for calculating income taxes in an interim period and the recognition of deferred tax liabilities for outside basis differences. The new guidance also simplifies aspects of the accounting for franchise taxes and enacted changes in tax laws or rates and clarifies the accounting for transactions that result in a step-up in the tax basis of goodwill. The standard is effective for annual periods beginning after December 15, 2020 and interim periods within, with early adoption permitted. Adoption of the standard requires certain changes to be made prospectively, with some changes to be made retrospectively. The Company does not expect the adoption of ASU 2019-12 to have a material impact on the Company's financial position, results of operations and cash flows.

3. Accrued Expenses

Accrued expenses consisted of the following:

	December 31, 2020	December 31, 2019
Research and development costs	$ 5,815	$ 8,059
Professional fees	648	1,439
Payroll related	5,916	3,655
Other	180	377
Accrued expenses	$ 12,559	$ 13,530

4. Fair Value of Financial Assets

As of December 31, 2020 and 2019, the carrying amount of cash and cash equivalents and short-term investments was $172,792 and $292,459, respectively, which approximates fair value. Cash and cash equivalents and short-term investments includes investments in U.S. treasury securities and money market funds that invest in U.S. government securities that are valued using quoted market prices. Accordingly, money market funds and government funds are categorized as Level 1. The financial assets valued based on Level 2 inputs consist of corporate debt securities and commercial paper, which consist of investments in highly-rated investment-grade corporations.

The following tables present information about the Company's financial assets measured at fair value on a recurring basis and indicate the level of the fair value hierarchy utilized to determine such fair values:

	Fair value Measurements as of December 31, 2020 using:			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash Equivalents:				
Corporate Debt Securities and Commercial Paper	$ —	$ 36,242	$ —	$ 36,242
U.S. Treasury Securities and Money Market Funds	63,182	—	—	63,182
Marketable Securities:				
Corporate Debt Securities and Commercial Paper	—	71,938	—	71,938
Total	$ 63,182	$ 108,180	$ —	$ 171,362

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

Marketable Securities

The following tables summarize the Company's marketable securities:

	December 31, 2020			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Assets				
Corporate debt securities and commercial paper (due within 1 year)	$ 71,895	$ 43	$ —	$ 71,938
	$ 71,895	$ 43	$ —	$ 71,938

	December 31, 2019			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Assets				
Corporate debt securities and commercial paper (due within 1 year)	$ 230,155	$ 54	$ (44)	$ 230,165
	$ 230,155	$ 54	$ (44)	$ 230,165

5. Right Of Use Asset and Lease Liability

The Company has a material operating lease for its head office facility and other immaterial operating leases for certain equipment. The Company’s office lease has a remaining lease term of 4.6 years. The Company measured the lease liability associated with the office lease using a discount rate of 10% at inception. The Company estimated the incremental borrowing rate for the leased asset based on a range of comparable interest rates the Company would incur to borrow an amount equal to the lease payments on a collateralized basis over a similar term in a similar economic environment. As of December 31, 2020, the Company has not entered into any lease arrangements classified as a finance lease.

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

Upon adoption of ASC 842, the Company elected the transition relief package, permitted within the standard, pursuant to which the Company did not reassess the classification of existing leases, whether any expired or existing contracts contain a lease, and whether existing leases have any initial direct costs. The Company also elected the practical expedient of not separating lease components from non-lease components for all leases. There was no cumulative-effective adjustment to the opening balance of retained earnings. The Company reviews all material contracts for embedded leases to determine if they have a right-of-use asset.

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

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

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

The Company's corporate headquarters is located in Boston, Massachusetts. This facility houses the Company's research, clinical, regulatory, commercial and administrative personnel. The Company's lease agreement commenced May 2019 and has a term of six years with a five-year renewal option to extend the lease. As of January 1, 2019, the Company did not included the five-year renewal option to extend the lease in its measurement of the ROU asset or lease liability. Rent expense, or operating lease costs, for the years ended December 31, 2020, 2019 and 2018 were $551, $629 and $359, respectively.

Supplemental cash flow information related to the Company's lease for the year ended December 31, 2020, includes cash payments of $786 used in the measurement of its operating lease liability.

The following table presents the maturities of the Company's operating lease liability related to office space as of December 31, 2020, all of which is under a non-cancellable operating lease:

	Operating Lease
2021	$ 802
2022	818
2023	834
2024	851
2025	502
Thereafter	—
Total operating lease payments	3,807
Less: imputed interest	721
Total operating lease liability	$ 3,086

6. Common Stock

Common Stock

On April 3, 2018, in association with the Takeda license agreement, the Company issued 223,544 shares of common stock. See Note 8 for further discussion.

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

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

7. Stock-based Compensation

2017 Equity Incentive Plan

The 2017 Plan provides for the grant of incentive and non-qualified stock options, stock appreciation rights, performance units, restricted stock, restricted stock units and stock grants to employees, consultants, advisors and directors of us or our affiliates, as determined by the board of directors. The number of shares authorized under the 2017 Plan will be increased each January 1, commencing on January 1, 2018 and ending on (and including) January 1, 2027, by an amount equal to 4% of the outstanding shares of stock outstanding as of the end of the immediately preceding fiscal year. On January 1, 2021, 2020 and 2019, 1,769,436, 1,759,870 and 1,376,429 shares, respectively, were added to the 2017 Plan. Notwithstanding the foregoing, the board of directors may act prior to January 1 for a given year to provide that there will be no such January 1 increase in the number of shares authorized under the 2017 Plan for such year, or that the increase in the number of shares authorized under the 2017 Plan for such year will be a lesser number than would otherwise occur pursuant to the preceding sentence. Shares of common stock issued upon exercise of stock options are generally issued from new shares of the Company. The 2017 Plan provides that the exercise price of incentive stock options cannot be less than 100% of the fair market value of the common stock on the date of the award for participants who own less than 10% of the total combined voting power of stock of the Company, and not less than 110% for participants who own more than 10% of the Company's voting power. Awards granted under the 2017 Plan will vest over periods as determined by the Company's board of directors. For options granted to date, the exercise price equaled the fair value of the common stock as determined by the board of directors on the date of grant.

As of December 31, 2020, an aggregate of 7,484,536 shares of common stock were authorized for issuance under the 2017 Plan, of which a total of approximately 2,108,764 shares of common stock remained available for future

awards. In addition, a total of 5,375,772 shares of common stock reserved for issuance were subject to currently outstanding stock options and restricted stock units granted under the Plan.

The Company estimates the fair value of stock option awards to employees and non-employees using the Black-Scholes option-pricing model, which requires the input of subjective assumptions, including (a) the expected volatility of the underlying common stock, (b) the expected term of the award, (c) the risk-free interest rate, and (d) expected dividends. Due to the lack of a public market for the trading of its common stock and a lack of company-specific historical and implied volatility data, the Company has based its estimate of expected volatility on the historical volatility of a group of companies in the pharmaceutical and biotechnology industries in a similar stage of development as the Company that are publicly traded. For these analyses, the Company selected companies with comparable characteristics to its own including enterprise value, risk profiles and with historical share price information sufficient to meet the expected life of the stock-based awards. The Company computes the historical volatility data using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of its stock-based awards. During 2020, the Company began to estimate its volatility by using a blend of its stock price history for the length of time it has market data for its stock and the historical volatility of similar public companies for the expected term of each grant. The Company will continue to apply this process until a sufficient amount of historical information regarding the volatility of its own stock price becomes available.

The Company estimated the expected life of its employee stock options using the “simplified” method, whereby, the expected life equals the average of the vesting term and the original contractual term of the option. The risk-free interest rates for periods within the expected life of the option are based on the U.S. Treasury yield curve in effect during the period the options were granted. We have elected to account for forfeitures as they occur.

The grant date fair value of awards subject to service-based vesting is recognized ratably over the requisite service period, which is generally the vesting period of the respective awards. The Company's stock option awards typically vest over a service period that ranges from one to four years and includes awards with one year cliff vesting followed by ratable monthly and quarterly vesting thereafter and ratable monthly and quarterly vesting beginning on the grant date.

During the years ended December 31, 2020, 2019 and 2018, the Company granted 2,546,075, 1,445,200 and 1,218,790 stock option awards to certain directors, employees and non-employees, respectively. Using the Black-Scholes option pricing model, the weighted-average grant date fair value relating to outstanding stock options granted under the Company’s stock option plan during the years ended December 31, 2020, 2019 and 2018 was $13.25, $17.19 and $17.27, respectively. The total intrinsic value of stock options exercised during the years ended December 31, 2020, 2019 and 2018 was $2,661, $3,844 and $7,980, respectively.

The fair value of stock options granted to employees and directors was estimated at the date of grant using the Black-Scholes option pricing model with the following weighted-average assumptions:

	Year ended December 31,		
	2020	2019	2018
Risk-free interest rate	0.76 %	2.40 %	2.73 %
Expected term (in years)	6.08	6.07	5.89
Expected volatility	70.67 %	66.03 %	62.21 %
Expected dividend yield	—	—	—

The Company early adopted ASU 2018-07, *Improvements to Nonemployee Share-Based Payment Accounting (Topic 718),* in July 2018. The guidance was adopted using the modified-retrospective approach, which requires that unsettled equity-classified awards for which a measurement date has not been established be measured using the adoption

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

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

A summary of the Company's stock option activity for the year ended December 31, 2020 is as follows:

	Number of Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term	Aggregate Intrinsic Value
Outstanding as of December 31, 2019	3,428,497	$ 21.17	7.94	$ —
Granted	2,546,075	21.22	—	—
Exercised	(184,098)	8.07	—	2,661
Cancelled	(591,239)	24.34	—	—
Outstanding as of December 31, 2020	5,199,235	$ 21.30	7.57	$ 45,233
Options vested and expected to vest as of December 31, 2020	5,199,235	$ 21.30	7.57	$ 45,233
Options exercisable at December 31, 2020	2,157,915	$ 18.95	5.47	$ 24,218

A summary of the Company's restricted stock unit activity for the year ended December 31, 2020 is as follows:

	Number of RSU's	Weighted-Average Grant Date Fair Value
Unvested as of December 31, 2019	—	$ —
Granted	209,912	19.77
Vested	(25,000)	22.30
Cancelled	(8,375)	17.87
Unvested as of December 31, 2020	176,537	$ 19.50

As of December 31, 2020, the aggregate intrinsic value of non-vested RSUs was $5,248.

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

	Year Ended December 31,		
	2020	2019	2018
Research and development	$ 6,055	$ 5,163	$ 2,793
Selling, general, and administrative	11,400	6,712	3,597
Total	$ 17,455	$ 11,875	$ 6,390

Stock-based compensation expense by award type recognized during the years ended December 31, 2020, 2019 and 2018 was as follows:

	Year Ended December 31,		
	2020	2019	2018
Stock options	$ 15,915	$ 11,667	$ 6,241
Employees stock purchase plan	180	208	65
Restricted stock units	1,360	—	84
Total	$ 17,455	$ 11,875	$ 6,390

During 2020 and 2019, there were certain awards subject to modification accounting. Per terms of separation with a former employee, the employee's stock option awards were amended to provide for accelerated vesting and extended time to exercise vested options. As a result, the Company recognized incremental expense for the stock option awards of $2,880 and $56, respectively.

As of December 31, 2020, the Company has unrecognized compensation cost of $39,111 related to non-vested employee, non-employee and director stock option awards that is expected to be recognized over a weighted-average period of 2.83 years. The Company has unrecognized compensation cost of $2,640 related to non-vested employee restricted stock unit awards that is expected to be recognized over a weighted-average period of 2.52 years.

2017 Employee Stock Purchase Plan

The Company has a 2017 Employee Stock Purchase Plan, or the 2017 ESPP, which became effective in connection with the completion of the Company's IPO in October 2017. As of December 31, 2020, a total of 1,000,993 shares of common stock were reserved for issuance under the 2017 ESPP. In addition, the number of shares authorized under the 2017 ESPP will be increased each January 1, commencing on January 1, 2019 and ending on (and including) January 1, 2027, by an amount equal to the lesser of 1% of outstanding shares as of the end of the immediately preceding fiscal year. On January 1, 2020 and 2019, 439,968 and 344,107 shares, respectively, were added to the 2017 ESPP. Notwithstanding the foregoing, the board of directors may act prior to January 1 of a given year to provide that there will be no such January 1 increase in the number of shares authorized under the 2017 ESPP for such year, or that the increase in the number of shares authorized under the 2017 ESPP for such year will be a lesser number than would otherwise occur pursuant to the preceding sentence. The board of directors elected not to increase the pool on January 1, 2021. During the year ended December 31, 2020, 30,052 shares were issued under this plan.

8. Significant Agreements

License Agreements

Pursuant to a license agreement with Ipsen Pharma, S.A.S., or Ipsen, the Company has an exclusive, sublicensable, worldwide license to certain patents and other intellectual property rights to research, develop, and commercialize compounds that were discovered or researched by Ipsen in the course of conducting its MC4R program or that otherwise were covered by the licensed patents. Under the terms of the setmelanotide Ipsen license agreement, assuming that setmelanotide is successfully developed, receives regulatory approval and is commercialized, Ipsen may receive aggregate payments of up to $40,000 upon the achievement of certain development and commercial milestones and royalties on future product sales in the mid-single digits. Substantially all of such aggregate payments of up to $40,000 are for milestones that may be achieved no earlier than first commercial sale of setmelanotide. In the event that the Company executes a sublicense agreement, it shall make payments to Ipsen, depending on the date of such sublicense agreement, ranging from 10% to 20% of all revenues actually received under such sublicense agreement.

The Company has recorded milestone expenses related to this license agreement of $3,000 and $1,000 during the years ended December 31, 2020 and 2018, respectively. The expenses were recorded as research and development

expenses when the milestone criterias were met in full. No milestone expenses were recorded during the year ended December 31, 2019.

In January 2016, the Company entered into a license agreement with Camurus AB, or Camurus, for the use of Camurus' drug delivery technology. The contract includes a non-refundable and non-creditable signing fee of $500. The Camurus agreement also includes up to $7,750 in one-time, non-refundable development milestones achievable upon certain regulatory successes. The Company is also required to pay to Camurus, mid to mid-high single digit royalties, on a product-by-product and country-by-country basis of annual net sales, until the later of (i) 10 years after the date of first commercial sale of such product in such country; or (ii) the expiration of the last to expire valid claim of all licensed patent rights in such country covering such product. The Company is also required to pay one-time, non-refundable, non-creditable sales milestones upon the achievement of certain sales levels for such product that cannot be in excess of $57,000.

In March 2018, the Company entered into a license agreement with Takeda, for the rights of a program that includes the clinical candidate RM-853, which is a GOAT inhibitor, which is currently in preclinical development for PWS. Pursuant to the license agreement the Company was required to pay a non-refundable and non-creditable signing fee, which the Company settled by issuing on April 3, 2018, 223,544 shares of common stock valued at $4,448. Under the terms of the license agreement, assuming that RM-853 is successfully developed, receives regulatory approval and is commercialized, the Company is also required to pay up to $70,000 in one-time, non-refundable development milestone payments upon the achievement of certain clinical and regulatory milestones. The Company is also required to pay up to $70,000 in one-time, non-refundable, non-creditable sales milestone payments upon the achievement of certain sales levels. The Company is also required to pay to Takeda, mid to mid-high single digit royalties (subject to certain potential reductions over time), on a product-by-product and country-by-country basis of annual net sales, of each product in such country, beginning on the first commercial sale of a product in such country, and continuing until the latest of (i) 10 years after the date of first commercial sale of such product in such country; or (ii) the expiration of the last to expire valid claim of a Takeda patents covering the composition or use of such product in such country; or (iii) the expiration of all regulatory exclusivity for such product in such country. The Company recorded the fair value of the common stock to be issued to the licensors as research and development expense, as the license does not have a future alternative use, in accordance with ASC Topic 730, *Research and Development.*

9. Commitments and Contingencies

Legal Proceedings

The Company, from time to time, may be party to litigation arising in the ordinary course of business. The Company was not subject to any material legal proceedings during the years ended December 31, 2020, 2019 and 2018 and to the best of its knowledge, no material legal proceedings are currently pending or threatened.

Other

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

Based on the Company's current development plans as of December 31, 2020, potential payments due to third parties during the next 12 months from the filing of this Annual Report on Form 10-K are estimated be approximately $9,000 in commercial milestones, in connection with our license agreements. These milestones generally become due and payable upon achievement of such milestones or sales. When the achievement of these milestones or sales have not occurred, such contingencies are not recorded in the Company's consolidated financial statements.

10. Related-Party Transactions

Expenses paid directly to consultants and vendors considered to be related parties amounted to $3,221, $2,489 and $2,005 for the years ended December 31, 2020, 2019 and 2018, respectively. Outstanding payments due to these related parties as of December 31, 2020 and 2019 were $187 and $264, respectively and were included within accounts payable on the balance sheet.

11. Income Tax

For the years ended December 31, 2020, 2019 and 2018 the Company did not have a current or deferred income tax expense or benefit as the entity has incurred losses since inception and has provided a full valuation allowance against its deferred tax assets.

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

	As of December 31,		
	2020	2019	2018
Statutory tax rate	21.00 %	21.00 %	21.00 %
State tax, net of federal benefit	6.32 %	6.75 %	6.90 %
Research and development credit	1.46 %	2.49 %	1.52 %
Orphan drug credit	2.40 %	1.85 %	1.95 %
Tax law change	— %	— %	— %
Stock compensation	(0.53)%	(0.10)%	0.46 %
Investor instrument revaluation	— %	— %	— %
Other	(0.30)%	0.20 %	0.05 %
Change in valuation allowance	(30.35)%	(32.19)%	(31.88)%
Effective tax rate	— %	— %	— %

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

	As of December 31,	
	2020	2019
Deferred tax assets:		
Net operating loss carryforwards	$ 102,367	$ 71,524
Research and development credits	10,347	7,876
Orphan drug credit	10,110	6,889
Capitalized license fee	2,492	1,734
Stock-based compensation	6,621	3,628
Accrued expenses and other	2,267	2,006
Total deferred tax assets	134,204	93,657
Valuation allowance	(133,596)	(92,943)
Net deferred tax assets	608	714
Deferred tax liabilities:		
Operating lease right-of-use asset and other	(608)	(714)
Total deferred tax liabilities	$ (608)	$ (714)

ASC 740 requires a valuation allowance to reduce the deferred tax assets reported if, based on the weight of available evidence, it is more likely than not that some portion or all of the deferred tax assets will not be realized. After consideration of all the evidence, both positive and negative, the Company has recorded a full valuation allowance against its deferred tax assets at December 31, 2020 and 2019, because the Company's management has determined that is it more likely than not that these assets will not be realized. The increase in the valuation allowance of $40,653 in 2020 and $45,264 in 2019 primarily relates to the net loss incurred by the Company during each period.

As of December 31, 2020, the Company had federal and state net operating loss carryforwards of approximately $382,314 and $351,187, respectively, which are available to reduce future taxable income. The net operating loss carryforwards expire at various times beginning in 2033 for federal and state purposes. Of the federal net operating loss carryforwards at December 31, 2020, $309,147 can be carried forward indefinitely.

As of December 31, 2020, the Company had federal and state research tax credits of approximately $8,115 and $2,826, respectively, which may be used to offset future tax liabilities. Additionally, as of 2020, the Company had a federal orphan drug credit related to qualifying research of $10,110. These tax credit carryforwards will begin to expire at various times beginning in 2033 for federal purposes and 2028 for state purposes.

The net operating loss and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. Net operating loss and tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant stockholders over a three-year period in excess of 50%, as defined under Sections 382 and 383 of the Internal Revenue Code, respectively, as well as similar state provisions and other provisions within the Internal Revenue Code. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years.

The Company has not recorded any reserves for uncertain tax positions as of December 31, 2020 and 2019. The Company has not, as yet, conducted a study of research and development credit carryforwards. This study may result in an adjustment to the Company's research and development credit carryforwards; however, until a study is completed and any adjustment is known, no amounts are being presented as an uncertain tax position. A full valuation allowance has been provided against the Company's research and development credits and, if an adjustment is required, this adjustment would be offset by an adjustment to the valuation allowance. Thus, there would be no impact to the balance sheets or statements of operations and comprehensive loss if an adjustment were required.

In March 2020, the Coronavirus Aid, Relief, and Economic Security Act, the CARES Act, was signed into law. The CARES Act includes provisions relating to several aspects of corporate income taxes. The CARES Act did not have a significant impact on the Company’s provision for income taxes.

Interest and penalty charges, if any, related to unrecognized tax benefits will be classified as income tax expense in the accompanying statements of operations and comprehensive loss. As of December 31, 2020 and 2019, the Company had no accrued interest or penalties related to uncertain tax positions.

The Company is subject to examination by the U.S. federal, state and local income tax authorities for tax years 2013 forward. The Company is not currently under examination by the Internal Revenue Service or any other jurisdictions for any tax years.

12. Subsequent Events.

The Company considers events or transactions that occur after the balance sheet date but prior to the issuance of the financial statements to provide additional evidence for certain estimates or to identify matters that require additional disclosure. Subsequent events have been evaluated as required. The Company has evaluated all subsequent events and determined that there are no material recognized or unrecognized subsequent events requiring disclosure, other than as disclosed with the above notes to these consolidated financial statements and below.

On January 5, 2021, the Company entered into a definitive agreement to sell its PRV, for $100,000. The PRV was granted to the Company by the U.S. FDA with the approval of IMCIVREE for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to POMC, PCSK1 or LEPR deficiency confirmed by genetic testing. The sale closed on February 17, 2021.

On February 9, 2021 the Company completed a public offering of 5,750,000 shares of common stock at an offering price of $30.00 per share, which included the exercise in full by the underwriters of their option to purchase up to 750,000 additional shares of common stock. The Company received approximately $161,550 in net proceeds after deducting underwriting discounts, commissions and estimated offering expenses.

The financial statements as of December 31, 2020, including share and per share amounts, do not include the effects of the PRV sale or the February public offering.

Exhibit 10.5

Summary of Non-Employee Director Compensation Policy

Under the Company's non-employee director compensation policy, all non-employee directors will be paid an annual retainer fee of $45,000 and such additional fees as are set forth in the following table. All payments will be made quarterly in arrears.

Non-Employee Director	Annual Fee
Lead Director	$ 25,000
Non-Executive Chair	$ 30,000
Chairman of the audit committee	$ 20,000
Member of the audit committee (other than chairman)	$ 10,000
Chairman of the compensation committee	$ 15,000
Member of the compensation committee (other than chairman)	$ 7,500
Chairman of the governance and nominating committee	$ 10,000
Member of the governance and nominating committee (other than chairman)	$ 5,000

Under the policy, each individual who is initially appointed or elected to the board of directors will be eligible to receive an option to purchase up to 30,000 shares of our common stock under the 2017 Equity Incentive Plan on the date he or she first becomes a non-employee director. These option grants will vest annually over a three-year period from the date of grant, subject to continued service as a non-employee director through that vesting date. In addition, on the date of the annual meeting of stockholders, each continuing non-employee director who has served on the board of directors for a minimum of six months will be eligible to receive an option grant to purchase up to 15,000 shares of our common stock, which will vest in full upon the earlier of the first anniversary of the date of grant or the date of the next annual meeting of stockholders. The exercise price for each of these option grants will be equal to the fair market value of our common stock on the date of grant. These new director grants and annual grants will be subject to approval by our board of directors at the time of grant. The share numbers set forth herein will be appropriately adjusted for any split or recapitalization of the Company's securities.

rhythm

Rhythm Pharmaceuticals, Inc.
500 Boylston Street - 11th Floo!"
Boston, MA 02116
Main Telephone: 617-585-2090
www.rhythmtx.com

May 10, 2018

Simon Kelner

Dear Simon:

On behalf of Rhythm Pharmaceuticals, Inc., (the "Company" or "Rhythm"), I am pleased to set forth below the terms of your employment with the Company.

Employment. You will be employed as Chief Human Resources Officer, beginning on June 4, 2018 (the "Start Date"), reporting to Keith Gottesdiener, CEO. During the term of your employment with the Company, you will be responsible for performing the duties associated with the position above or as the Company may otherwise assign to you. Your primary place of employment initially will be in the Company's offices located in Massachusetts; however, you will be expected to travel as may be necessary to fulfill your responsibilities. In the course of your employment with the Company, you will be subject to, and required to comply with, all Company policies and all applicable laws and regulations.

Base Salary. During your employment, your salary will be $310,000 annualized, subject to all required and elected taxes and other withholdings. Your salary may be adjusted from time to time in accordance with normal business practice and in the sole discretion of the Company.

Annual Incentive Bonus. Following the end of each fiscal year and subject to the approval by the Company's Board of Directors in its sole discretion, you will be eligible to earn an incentive bonus, based on your performance and the Company's performance, each during the applicable fiscal year, if your employment continues in good standing on the date of payment of such incentive bonus. Your target annual incentive bonus opportunity shall be 35% of your annualized base salary.

Equity Grant. Subject to and upon the approval of the Board of Directors of the Company after your Start Date, the Company shall grant to you a stock option (the "Option") under the Company's 2017 Equity Incentive Plan, as it may be amended from time to time (the "Plan"), to purchase 60,000 shares (subject to any adjustments for any stock splits, stock dividends, reverse stock splits or recapitalizations that are effected at any time during the period commencing after the date of this offer letter and ending on the grant date of the Option, the "Option Shares") of the Company's common stock, $0.001 par value per share (the "Common Stock"), at an exercise price equal to fair market value of the Common Stock, as determined by the Board of Directors of the Company, on the date of the grant of the Option (the "Grant

Date"). Promptly after the Grant Date, the Company and you shall execute and deliver to each other the Company's then standard form of stock option agreement, evidencing the Option and the terms thereof. The Option shall be subject to, and governed by, the terms and provisions of the Plan and your stock option agreement.

Subject to the terms and conditions set forth below in this letter of employment and unless the Board of Directors of the Company shall otherwise determine on the Grant Date, the Option shall be exercisable for twenty-five percent (25%) of the Option Shares as of the first anniversary of your Start Date, and the remainder of the Option Shares shall become exercisable thereafter in a series of twelve (12) equal quarterly installments until such Option shall have become fully vested and exercisable.

Upon termination of your employment with the Company, you may exercise the Option to the extent then outstanding and exercisable, but only until the earlier to occur of (i) the expiration of the term of the Option and (ii) the expiration of the limited period of time set forth in the Plan and/or your stock option agreement for the exercise of the Option following termination of your employment with the Company.

Any Option Shares you acquire pursuant to the exercise of the Option shall be subject to the terms and restrictions on transfer set forth in the Plan. your stock option agreements and any other agreement to which you shall become, or are required to become, a party pursuant to the terms of the Plan.

You may be awarded additional equity grants from time to time in accordance with normal business practice and in the sole discretion of the Company's Board of Directors. The terms of any future equity grant will be consistent with any plan under which they are granted and the terms of the applicable agreement under which the award(s) are granted.

Commuting and Relocation Expenses Allowance. Rhythm agrees to pay you $176,834.65 to reimburse you for travel, commuting, lodging, and other relocation expenses (including moving your family to Boston if you decide to do so) for a period of eighteen months commencing after your Start Date. Such $176,834.65 will be paid to you by the Company in four equal installments of $44,208.66 in accordance with the Company's ordinary payroll practices on the first payroll date following: your Start Date, and the six-month, twelve-month, and eighteen-month anniversary of your Start Date, so long as you are still employed by the Company on the date of disbursement of the payment. You acknowledge that this relocation expenses allowance will be taxable to you.

Benefits. You may participate in any and all benefit programs that the Company establishes and makes available to its employees from time to time, subject to the terms and conditions of those programs. The Company's benefits programs are subject to change at any time in the Company's sole discretion.

Vacation. You will be entitled to annual paid vacation of four (4) weeks. Your accrual and use of vacation time will be pursuant and subject to any vacation or time off policy the Company may establish or modify from time to time. The Company's vacation policy is subject to change at any time in the Company's sole discretion.

Severance. If the Company terminates your employment without Cause (as defined below) or you resign your employment with the Company for Good Reason (as defined below) (in either event, a "Qualifying Termination"), then, subject to your execution of a release acceptable to the Company (the "Release"), the expiration of any revocation period provided in the Release and your continued compliance with the terms of the NDA (as defined below), the Company will provide severance pay to you in an amount equal to your then-current base salary rate for a period of nine (9) months (the "Regular Severance Amount"). However, if such a Qualifying Termination occurs on or prior to the first anniversary of the Start Date, the Regular Severance Amount will be an amount equal to your then-current base salary rate for a period of twelve (12) months.

If there is a Qualifying Termination within the three (3) months immediately preceding or the twelve (12) months immediately following a Change of Control (as such term is defined in the Plan), then, subject to your execution of a Release following your Separation from Service (as defined below), the expiration of any revocation period provided in the Release and your continued compliance with the terms of the NDA, the Company will, in lieu of the Regular Severance Amount, provide you with severance pay in an amount (the "Change of Control Severance Amount"} equal to your then-current base salary rate for a period of twelve (12) months plus an amount equal to 100% of your then-applicable target annual incentive bonus for the fiscal year in which such Qualifying Termination occurs, which then-applicable target annual incentive bonus amount shall be payable by the Company in equal installments during such twelve (12) month period at the same time that the Company is required to make payment of such monthly base salary payments during such twelve (12) month period.

Any severance amount to which you may be entitled under this letter will be paid in substantially equal installments in accordance **with** the Company's ordinary payroll practices, beginning on the first payroll date following the date that is either (i) sixty (60) days after the date of your Separation from Service, or (ii) in the case of a Separation from Service that is a Qualifying Termination that occurs within the three (3) months immediately preceding a Change of Control, sixty (60) days after the date of such Change of Control, provided that, in the case of either of the foregoing clauses (i) and (ii), the Company, in its sole discretion, may have the option to pay any such severance amount to you as a lump sum. To be eligible for either the Regular Severance Amount or the Change of Control Severance Amount, as applicable, you must execute and deliver the Release to the Company and allow it to become effective within thirty (30) days of your Separation from Service or, if later, within thirty (30) days of a Change of Control giving rise to a Change of Control Severance Amount entitlement.

In addition, if following your Separation from Service, you are eligible for and timely elect continued medical insurance coverage pursuant to COBRA, the Company will reimburse you for the applicable premiums for you and your eligible dependents during the period commencing on the date of your Separation from Service and ending on the earlier to occur of (a) the final day of the applicable severance period and (b) the date you otherwise become ineligible for continued coverage under COBRA. Notwithstanding the foregoing, if the Company determines that it cannot provide such reimbursement of premiums to you without potentially violating applicable law, the Company shall not be obligated to make any such payments or reimbursements to you.

If the Qualifying Termination occurs at any time within the three (3) months immediately preceding or the twelve (12) months immediately following a Change of Control, then each outstanding

equity award in the Company held by you (including, without limitation, the Option) shall immediately vest and, if applicable, become exercisable with respect to one hundred percent (100%) of the shares of equity of the Company subject thereto. The foregoing provisions of this paragraph shall apply notwithstanding anything express or implied to the contrary in any agreement or award between you and the Company, or in any plan of the Company, that is applicable to such outstanding equity award.

409A Matters. Notwithstanding anything herein to the contrary, in the event that any compensation or benefit that constitutes "nonqualified deferred compensation" within the meaning of Section 409A of the Internal Revenue Code of 1986, as amended (the "Code"), becomes payable upon the occurrence of a Change of Control, such compensation or benefit shall not be paid unless such Change of Control constitutes a "change in control event" within the meaning of Section 409A of the Code.

Withholding Taxes. All payments and benefits described in this letter agreement or that you may otherwise be entitled or eligible to receive as a result of your employment with the Company will be subject to applicable federal, state and local tax withholdings.

280G Matters. If any payment or benefit you would receive under this letter, when combined with any other payment or benefit you receive pursuant to the termination of your employment with the Company ("Payment") would (i) constitute a "parachute payment" within the meaning of Section 280G of the Code, and (ii) but for this sentence, be subject to the excise tax imposed by Section 4999 of the Code (the "Excise Tax"), then such Payment shall be either (x) the full amount of such Payment or (y) such lesser amount (with your choice of whether to reduce cash payments or stock option compensation or both) as would result in no portion of the Payment being subject to the Excise Tax, whichever of the foregoing amounts, taking into account the applicable federal, state and local employment taxes, income taxes and the Excise Tax results in your receipt, on an after-tax basis, of the greater amount of the Payment notwithstanding that all or some portion of the Payment may be subject to the Excise Tax.

Definitions

Separation from Service. For purposes of this letter, "Separation from Service" means a "separation from service" within the meaning of Section 409A of the Code. Each installment payment provided under this letter shall at all times be considered a separate and distinct payment for purposes of Section 409A of the Code. Notwithstanding anything in this letter to the contrary, to the extent required to avoid a prohibited distribution under Section 409A of the Code, the benefits provided under this letter will not be provided to you until the earlier of (a) the expiration of the six-month period measured from the date of your Separation from Service with the Company or (b) the date of your death. Upon the first business day after expiration of the relevant period, all payments delayed pursuant to the preceding sentence will be paid in a lump sum and any remaining payments due will be paid as otherwise provided herein.

Cause. "Cause" shall mean the occurrence of any of the following events by the individual: (i) commission of any crime involving the Company, or any crime involving fraud, breach of trust, or physical or emotional harm to any person, moral turpitude or dishonesty; (ii) any unauthorized use or disclosure of the Company's proprietary information (other than any such use or disclosure that is not intentional and is not material); (iii) any intentional misconduct or gross negligence that has a material adverse effect on the Company's business or reputation; (iv) any material

breach by you of any agreement between you and the Company that is not cured within thirty (30) days after receipt of written notice from the Company describing any such breach; or (v) repeated and willful failure to perform the duties, functions and responsibilities of the individual's position after a written warning from the Company.

Good Reason. "Good Reason" shall mean your resignation from all positions you then hold with the Company if: (A) without your written consent (i) there is a material diminution in the nature or scope of your responsibilities, duties, authority, or title; (ii) there is a material reduction of your base salary; provided, however, that a material reduction in your base salary pursuant to a salary reduction program affecting all or substantially all of the employees of the Company and that does not adversely affect you to a greater extent than other similarly situated employees shall not constitute Good Reason; or (iii) you are required to relocate your primary work location to a facility or location that would increase your one way commute distance by more than thirty-five (35) miles from your primary work location as of immediately prior to such change, (B) you provide written notice outlining such conditions, acts or omissions to the Company's Chief Executive Officer, President, or General Counsel within thirty (30) days immediately following such material change or reduction, (C) such material change *or* reduction is not remedied by the Company within thirty (30) days following the Company's receipt of such written notice and (D) your resignation is effective not later than thirty (30) days after the expiration of such thirty (30) day cure period. "Good Reason" shall also mean your resignation, at your sole discretion, on the one-year anniversary of a Change of Control from all positions you then hold with the Company or its successor if by that date you have not entered into a written letter or agreement with the Company or such successor that provides for your continued employment with the Company or such successor. For purposes of clarification, any Qualifying Termination that occurs on the first anniversary of a Change of Control shall be deemed and treated as occurring within the twelve (12) months immediately following a Change of Control for all purposes of this letter.

Invention, Non-Disclosure, Non-Competition and Non-Solicitation Obligations. At or prior to the Start Date, you shall execute and deliver for the benefit of the Company the Employee Confidentiality, Assignment of Inventions, Non-Competition and Non-Solicitation Agreement in the form attached hereto as Exhibit A.

At-Will Employment. This letter shall not be construed as an agreement, either express or implied, to employ you for any stated term, and shall in no way alter the Company's policy of employment at-will. Similarly, nothing in this letter shall be construed as an agreement, either express or implied, to pay you any compensation or grant you any benefit beyond the end of your employment with the Company, except as otherwise explicitly set forth in this letter. This letter supersedes all prior understandings, whether written or oral, with respect to the subject matter of this letter.

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

Please indicate your acceptance of this letter agreement by signing below in the space provided for your signature.

Sincerely,

/S/ Keith Gottesdiener
Chief Executive Officer

The foregoing correctly sets forth the terms of my at-will employment with the Company. I am not relying on any representations other than those set forth above.

/s/ Simon Kelner Date 10th May 2018
Simon Kelner

Exhibit 10.15

rhythm

Rhythm Pharmaceuticals, Inc.
500 Boylston Street - 11th Floor
Boston, MA 02116
Main Telephone: 617-585-2090
www.rhythmtx.com

Sept 14, 2018

Dr. Murray Stewart

Dear Murray:

On behalf of Rhythm Pharmaceuticals, Inc., (the "Company" or "Rhythm"), I am pleased to set forth below the terms of your employment with the Company.

Employment. You will be employed as Chief Medical Officer, beginning on Oct 22, 2018 (the "Start Date"), reporting to Keith Gottesdiener, CEO. During the term of your employment with the Company, you will be responsible for performing the duties associated with the position above or as the Company may otherwise assign to you. Your primary place of employment initially will be in the Company's offices located in Massachusetts; however, you will be expected to travel as may be necessary to fulfill your responsibilities. In the course of your employment with the Company, you will be subject to, and required to comply with, all Company policies and all applicable laws and regulations.

Base Salary. During your employment, your salary will be $440,000 annualized, subject to all required and elected taxes and other withholdings. Your salary may be adjusted from time to time in accordance with normal business practice and in the sole discretion of the Company.

Annual Incentive Bonus. Following the end of each fiscal year and subject to the approval by the Company's Board of Directors in its sole discretion, you will be eligible to earn an incentive bonus, based on your performance and the Company's performance, each during the applicable fiscal year, if your employment continues in good standing on the date of payment of such incentive bonus. Your target annual incentive bonus opportunity shall be 35% of your annualized base salary.

Reimbursement. In recognition of potential direct transition costs to Rhythm the Company is willing to reimburse you up to a maximum of $50,000 at the first regularly scheduled payroll period of the Company which occurs after you provide evidence of the incurrence of such costs to you. Voluntary termination within the first twelve (12) months of employment will require repayment by you of such signing bonus, payable to Rhythm. Any reimbursements by the Company to you of any eligible expenses that are not excludable from your income for Federal income tax purposes (the "Taxable Reimbursements") shall be made by no later than the last day of the taxable year following the year in which the expense was incurred.

Equity Grant. Subject to and upon the approval of the Board of Directors of the Company after your Start Date, the Company shall grant to you a stock option (the "Option") under the Company's 2017 Equity Incentive Plan, as it may be amended from time to time (the "Plan"), to purchase 100,000 shares (subject to any adjustments for any stock splits, stock dividends, reverse stock splits or recapitalizations that are effected at any time during the period commencing after the date of this offer letter and ending on the grant date of the Option, the "Option Shares") of the Company's common stock, $0.001 par value per share (the "Common Stock"), at an exercise price equal to fair market value of the Common Stock, as determined by the Board of Directors of the Company, on the date of the grant of the Option (the "Grant Date"). Promptly after the Grant Date, the Company and you shall execute and deliver to each other the Company's then standard form of stock option agreement, evidencing the Option and the terms thereof. The Option shall be subject to, and governed by, the terms and provisions of the Plan and your stock option agreement.

Subject to the terms and conditions set forth below in this letter of employment and unless the Board of Directors of the Company shall otherwise determine on the Grant Date, the Option shall be exercisable for twenty-five percent (25%) of the Option Shares as of the first anniversary of your Start Date, and the remainder of the Option Shares shall become exercisable thereafter in a series of twelve (12) equal quarterly installments until such Option shall have become fully vested and exercisable.

Upon termination of your employment with the Company, you may exercise the Option to the extent then outstanding and exercisable, but only until the earlier to occur of (i) the expiration of the tenn of the Option and (ii) the expiration of the limited period of time set forth in the Plan and/or your stock option agreement for the exercise of the Option following termination of your employment with the Company.

Any Option Shares you acquire pursuant to the exercise of the Option shall be subject to the terms and restrictions on transfer set forth in the Plan, your stock option agreements and any other agreement to which you shall become, or are required to become, a party pursuant to the terms of the Plan.

You may be awarded additional equity grants from time to time in accordance with normal business practice and in the sole discretion of the Company's Board of Directors. The terms of any future equity grant will be consistent with any plan under which they are granted and the terms of the applicable agreement under which the award(s) are granted.

Benefits. You may participate in any and all benefit programs that the Company establishes and makes available to its employees from time to time, subject to the terms and conditions of those programs. The Company's benefits programs are subject to change at any time in the Company's sole discretion.

Vacation. You will be entitled to annual paid vacation of four (4) weeks. Your accrual and use of vacation time will be pursuant and subject to any vacation or time off policy the Company may establish or modify from time to time. The Company's vacation policy is subject to change at any time in the Company's sole discretion.

Severance. If the Company terminates your employment without Cause (as defined below) or you resign your employment with the Company for Good Reason (as defined below) (in either event, a "Qualifying Termination"), then, subject to your execution of a release acceptable to the Company (the "Release"), the expiration of any revocation period provided in the Release and your continued compliance

with the terms of the NDA (as defined below), the Company will provide severance pay to you in an amount equal to your then-current base salary rate for a period of nine (9) months (the "Regular Severance Amount"). However, if such a Qualifying Termination occurs on or prior to the first anniversary of the Start Date, the Regular Severance Amount will be an amount equal to your then-current base salary rate for a period of twelve (12) months.

If there is a Qualifying Termination within the three (3) months immediately preceding or the twelve (12) months immediately following a Change of Control (as such term is defined in the Plan), then, subject to your execution of a Release following your Separation from Service (as defined below), the expiration of any revocation period provided in the Release and your continued compliance with the terms of the NDA, the Company will, in lieu of the Regular Severance Amount, provide you with severance pay in an amount (the "Change of Control Severance Amount") equal to your then-current base salary rate for a period of twelve (12) months plus an amount equal to 100% of your then-applicable target annual incentive bonus for the fiscal year in which such Qualifying Termination occurs, which then-applicable target annual incentive bonus amount shall be payable by the Company in equal installments during such twelve (12) month period at the same time that the Company is required to make payment of such monthly base salary payments during such twelve (12) month period.

Any severance amount to which you may be entitled under this letter will be paid in substantially equal installments in accordance with the Company's ordinary payroll practices, beginning on the first payroll date following the date that is either (i) sixty (60) days after the date of your Separation from Service, or (ii) in the case ofa Separation from Service that is a Qualifying Termination that occurs within the three (3) months immediately preceding a Change of Control, sixty (60) days after the date of such Change of Control, provided that, in the case of either of the foregoing clauses (i) and (ii), the Company, in its sole discretion, may have the option to pay any such severance amount to you as a lump sum. To be eligible for either the Regular Severance Amount or the Change of Control Severance Amount, as applicable, you must execute and deliver the Release to the Company and allow it to become effective within thirty (30) days of your Separation from Service or, if later, within thirty (30) days of a Change of Control giving rise to a Change of Control Severance Amount entitlement.

In addition, if following your Separation from Service, you are eligible for and timely elect continued medical insurance coverage pursuant to COBRA, the Company will reimburse you for the applicable premiums for you and your eligible dependents during the period commencing on the date of your Separation from Service and ending on the earlier to occur of (a) the final day of the applicable severance period and (b) the date you otherwise become ineligible for continued coverage under COBRA. Notwithstanding the foregoing, if the Company determines that it cannot provide such reimbursement of premiums to you without potentially violating applicable law, the Company shall not be obligated to make any such payments or reimbursements to you.

If the Qualifying Termination occurs at any time within the three (3) months immediately preceding or the twelve (12) months immediately following a Change of Control, then each outstanding equity award in the Company held by you (including, without limitation, the Option) shall immediately vest and, if applicable, become exercisable with respect to one hundred percent (100%) of the shares of equity of the Company subject thereto. The foregoing provisions of this paragraph shall apply notwithstanding anything

express or implied to the contrary in any agreement or award between you and the Company, or in any plan of the Company, that is applicable to such outstanding equity award.

409A Matters. Notwithstanding anything herein to the contrary, in the event that any compensation or benefit that constitutes "nonqualified deferred compensation" within the meaning of Section 409A of the Internal Revenue Code of 1986, as amended (the "Code"), becomes payable upon the occurrence of a Change of Control, such compensation or benefit shall not be paid unless such Change of Control constitutes a "change in control event" within the meaning of Section 409A of the Code.

Withholding Taxes. All payments and benefits described in this letter agreement or that you may otherwise be entitled or eligible to receive as a result of your employment with the Company will be subject to applicable federal, state and local tax withholdings.

280G Matters. If any payment or benefit you would receive under this letter, when combined with any other payment or benefit you receive pursuant to the termination of your employment with the Company ("Payment") would (i) constitute a "parachute payment" within the meaning of Section 2800 of the Code, and (ii) but for this sentence, be subject to the excise tax imposed by Section 4999 of the Code (the "Excise Tax"), then such Payment shall be either (x) the full amount of such Payment or (y) such lesser amount (with your choice of whether to reduce cash payments or stock option compensation or both) as would result in no portion of the Payment being subject to the Excise Tax, whichever of the foregoing amounts, taking into account the applicable federal, state and local employment taxes, income taxes and the Excise Tax results in your receipt, on an after-tax basis, of the greater amount of the Payment notwithstanding that all or some portion of the Payment may be subject to the Excise Tax.

Definitions

Separation from Service. For purposes of this letter, "Separation from Service" means a "separation from service" within the meaning of Section 409A of the Code. Each installment payment provided under this letter shall at all times be considered a separate and distinct payment for purposes of Section 409A of the Code. Notwithstanding anything in this letter to the contrary, to the extent required to avoid a prohibited distribution under Section 409A of the Code, the benefits provided under this letter will not be provided to you until the earlier of (a) the expiration of the six-month period measured from the date of your Separation from Service with the Company or (b) the date of your death. Upon the first business day after expiration of the relevant period, all payments delayed pursuant to the preceding sentence will be paid in a lump sum and any remaining payments due will be paid as otherwise provided herein.

Cause. "Cause" shall mean the occurrence of any of the following events by the individual: (i) commission of any crime involving the Company, or any crime involving fraud, breach of trust, or physical or emotional harm to any person, moral turpitude or dishonesty; (ii) any unauthorized use or disclosure of the Company's proprietary information (other than any such use or disclosure that is not intentional and is not material); (iii) any intentional misconduct or gross negligence that has a material adverse effect on the Company's business or reputation; (iv) any material breach by you of any agreement between you and the Company that is not cured within thirty (30) days after receipt of written notice from the Company describing any such breach; or (v) repeated and willful

failure to perform the duties, functions and responsibilities of the individual's position after a written warning from the Company.

Good Reason. "Good Reason" shall mean your resignation from all positions you then hold with the Company if: (A) without your written consent (i) there is a material diminution in the nature or scope of your responsibilities, duties, authority, or title; (ii) there is a material reduction of your base salary; provided, however, that a material reduction in your base salary pursuant to a salary reduction program affecting all or substantially all of the employees of the Company and that does not adversely affect you to a greater extent than other similarly situated employees shall not constitute Good Reason; or (iii) you are required to relocate your primary work location to a facility or location that would increase your one way commute distance by more than thirty-five (35) miles from your primary work location as of immediately prior to such change, (B) you provide written notice outlining such conditions, acts or omissions to the Company's Chief Executive Officer, President, or General Counsel within thirty (30) days immediately following such material change or reduction, (C) such material change or reduction is not remedied by the Company within thirty (30) days following the Company's receipt of such written notice and (D) your resignation is effective not later than thirty (30) days after the expiration of such thirty (30) day cure period. "Good Reason" shall also mean your resignation, at your sole discretion, on the one-year anniversary of a Change of Control from all positions you then hold with the Company or its successor ifby that date you have not entered into a written letter or agreement with the Company or such successor that provides for your continued employment with the Company or such successor. For purposes of clarification, any Qualifying Termination that occurs on the first anniversary of a Change of Control shall be deemed and treated as occurring within the twelve (12) months immediately following a Change of Control for all purposes of this letter.

Invention, Non-Disclosure, Non-Competition and Non-Solicitation Obligations. At or prior to the Start Date, you shall execute and deliver for the benefit of the Company the Employee Confidentiality, Assignment of Inventions, Non-Competition and Non-Solicitation Agreement in the form attached hereto as Exhibit A.

At-Will Employment. This letter shall not be construed as an agreement, either express or implied, to employ you for any stated term, and shall in no way alter the Company's policy of employment at-will. Similarly, nothing in this letter shall be construed as an agreement, either express or implied, to pay you any compensation or grant you any benefit beyond the end of your employment with the Company, except as otherwise explicitly set forth in this letter. This letter supersedes all prior understandings, whether written or oral, with respect to the subject matter of this letter.

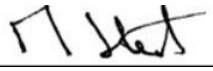
[The remainder of this page is intentionally left blank.]

Please indicate your acceptance of this letter agreement by signing below in the space provided for your signature.

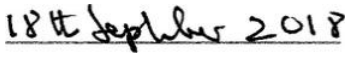
Sincerely,

/S/ Keith Gottesdiener
Chief Executive Officer

The foregoing correctly sets forth the terms of my at-will employment with the Company. I am not relying on any representations other than those set forth above.



Dr. Murray Stewart



Date

EXHIBIT A EXECUTED NDA

[See attached]

Rhythm
PHARMACEUTICALS

September 25, 2020

Jennifer Chien

Dear Jennifer,

Congratulations on your offer of employment with Rhythm Pharmaceuticals (also referred to in this letter as the **"Company").** I run confident you will find your career with Rhythm to be filled with opportunities, challenges and rewards. We take great pride in hiring professionals who have talent, drive, creativity and commitment and we are delighted to have you join our team. Below you will find important information about our organization, your individual position, rewards and benefits.

Employment. I am pleased to offer you the position of Executive Vice President, Head of North America, beginning on Oct 15, 2020 (the "Start Date"), reporting to David Meeker, President & CEO. You will be responsible for performing the duties associated with the position above or as the Company may otherwise assign to you. Your primary place of employment will initially be in the Company's offices located in Boston, Massachusetts; however, you will be expected to travel as may be necessary to fulfill your responsibilities. In the course of your employment with the Company, you will be subject to, and required to comply with, all Company policies and all applicable laws and regulations.

Base Salary . During your employment, your salary will be $395,000 annualized, subject to all required and elected taxes and other withholdings. Your salary may be adjusted from time to time in accordance with normal business practice and in the sole discretion of the Company.

Annual. Incentive Bonus. Following the end of each fiscal year and subject to the approval by the Company's Board of Directors in its sole discretion, you will be eligible to earn an incentive bonus based on your performance and the Company's performance, each during the applicable fiscal year, and subject to your continued employment in good standing on the date of payment of such incentive bonus. Your target annual incentive bonus opportunity shall be 40% of your annualized base salary.

Signing Bonus. The Company will pay you a one-time cash signing bonus of $!00,000 at the first regularly scheduled payroll period of tl1e Company which occurs after your Start Date. Voluntary termination (unless following a Change of Control) or termination for cause within the first twelve (12) months of employment will require repayment by you of such signing bonus, payable to Rhythm within 90 days of the termination date.

Equity Grant. Subject to and upon the approval of the Board of Directors of the Company after your Start Date, the Company shall grant to you a stock option (the "Option") under the Company's 2017 Equity Incentive Plan, as it may be amended from time to time (the "Plan") to purchase 100,000 shares (subject to any adjustments for any stock splits, stock dividends. reverse stock splits or recapitalization that are effected at any time during the period commencing after the date of this offer letter and ending on the grant date of the Option, the "Option Shares") of the Company's common stock, $0.001 par value per share (the " Common Stock"), at an exercise price equal to fair market value of the Common Stoc, k as determined by the Board of Directors of the Company, on the date of the grant of the Option (the "Grant Date") Promptly after the Grant Date, the Company and you shall execute and deliver to each other the Company's then standard form of stock option agreement, evidencing the Option and the terms thereof. The Option shall be subject to, and governed by, the terms and provisions of the Plan and your stock option agreement.

Subject to the terms and conditions set forth below in this letter of employment and 1mless the Board of Directors of the Company shall otherwise determine on the Grant Date, the Option shall be exercisable for twenty-five percent (25%) of 1he Option Shares as of the first anniversary of your Start Date, and the remainder of the Option Shares shall become exercisable thereafter in a series of twelve (12) equal quarterly installments until such Option shall have become fully vested and exercisable.

Upon termination of your employment with the Company, you may exercise the Option to the extent then outstanding and exercisable, but only until the earlier to occur of (i) the expiration of the term of the Option and (ii) the expiration of the limited period of time set forth in the Plan and/or your stock option agreement for the exercise of tile Option following termination of your employment with the Company.

Any Option Shares you acquire pursuant lo the exercise of the Option shall be subject to the terms and restrictions on transfer set forth in the Plan, your stock option agreements and any other

agreement to which you shall become, or are required to become, a party pursuant to the terms of the Plan.

You may be awarded additional equity grants from time to time in accordance with normal business practice and in the sole discretion of the Company's Board of Directors. The terms of any future equity grant will be consistent with any plan under which they are granted and the terms of the applicable agreement under which the award(s) are granted.

Benefits. You may participate in any and all benefit programs that the Company establishes and makes available to its employees from time to time, subject to the terms and conditions of those programs. The Company's benefits programs are subject to change at any time in the Company's sole discretion.

Vacation. You will be eligible to annual paid vacation of four (4) weeks, accrued over the course of the year and prorated based on your start date. Your accrual and use of vacation time will be pursuant and subject to any vacation or time off policy the Company may establish or modify from time to time. The Company's vacation policy is subject to change at any time in the Company's sole discretion.

Severance. If the Company terminates your employment without Cause (as defined below) or you resign your employment with the Company for Good Reason (as defined below) (in either event, a "'Qualifying Termination), then, subject to your execution of a release acceptable to the Company (the " "), the expiration of any revocation period provided in the Release and your continued compliance with the terms of the NDA (as defined below), the Company will provide severance pay to you in an amount equal to your then-current base salary rate for a period of nine (9) months (the "Regular Severance Amount"). However if such a Qualifying Termination occurs on or prior to the first anniversary of the Start Date, the Regular Severance Amount will be an amount equal to your then current base salary rate for a period of twelve (12) months.

If there is a Qualifying Termination within the three (3) months immediately preceding or the twelve (12) months immediately following a Change of Control (as such term is defined in the Plan), then, subject to your execution of a Release following your Separation from Service (as defined below), the expiration of any revocation period provided in the Release and your continued compliance with the terms of the NOA, the Company will, in lieu of the Regular Severance Amount, provide you with severance pay in an amount (the "Change of Control Severance Amount") equal to your then-current base salary rate for a period of twelve (12) months plus an amount equal to 100% of your then-applicable target annual incentive bonus for the fiscal year in which such Qualifying Termination occurs, which then-applicable target annual incentive bonus amount shall be payable by the Company in equal installments during such twelve (I 2) mouth period at the same time that the Company is required to make payment of such monthly base salary payments during such twelve (12) month period.

Any severance amount to which you may be entitled under this letter will be paid in substantially equal installments in accordance with the Company's ordinary payroll practices, beginning on the first payroll date following the date that is either (i) sixty (60) days after the date of your Separation from Service, or (ii) in the case of a Separation from Service that is a Qualifying Tem1ination that occurs within the three (3) months immediately preceding a Change of Control, sixty (60) days after the date of such Change of Control, provided that, in tl1e case of either of the foregoing clauses (i) and (ii), the Company, in its sole discretion, may have the option lo pay any such severance amount to you as a lump sum. To be eligible for either the Regular Severance Amount or the Change of Control Severance Amount as applicable, you must execute and deliver the Release to the Company and allow it to become effective within thirty (30) days of your Separation from Service ,or if later, within thirty (30) days of a Change of Control giving rise to a Change of Control Severance Amount entitlement.

In addition, if following your Separation from Service, you are eligible for and timely elect continued medical insurance coverage pursuant to COBRA, the Company will reimburse you for the applicable premiums for you and your eligible dependents during U1e period commencing on the date of your Separation from Service and ending on the earlier to occur of (a) the final day of the applicable severance period and (b) the date you otherwise become ineligible for continued coverage under COBRA.

Notwithstanding the foregoing, if the Company determines that it cannot provide such reimbursement of premiums to you without potentially violating applicable law, the Company shall not be obligated to make any such payments or reimbursements lo you.

If the Qualifying Termination occurs at any time within the throe (3) months immediately preceding or the twelve (12) months immediately following a Change of Control, then each outstanding equity award in the Company held by you (including, without limitation, the Option) shall immediately vest and, if applicable, become exercisable with respect to one hundred percent (100%) of the shares of equity of the Company subject thereto. The foregoing provisions of this paragraph shall apply notwithstanding anything express or implied to the contrary in any agreement or award between you and the Company, or in any plan of the Company, that is applicable to such outstanding equity award.

409A Matters. Notwithstanding anything herein to the contrary, in the event that any compensation or benefit that constitutes "nonqualified deferred compensation" within the meaning of Section 409A of the Internal Revenue Code of 1986, as amended (the " "), becomes payable upon the occurrence of a Change of Control, such compensation or benefit shall not be paid unless such change of

control constitutes a "change in control event" within the meaning of Section 409A or the Code.

Withholding Taxes. All payments and benefits described in this letter agreement or that you may otherwise be entitled or eligible to receive as a result of your employment with the Company will be subject to applicable federal. state and local tax withholdings.

280G Matters. If any payment or benefit you would receive under this letter, when combined with any other payment or benefit you receive pursuant to the termination of your employment with the Company **("Payment")** would (i) constitute a '·parachute payment" within the meaning of Section 2800 of the Code, and (ii) but for this sentence, be subject to the excise tax imposed by Section 4999 of the Code (the **"Excise Tax"),** then such Payment shall be either (x) the full amount of such Payment or (y) such lesser amount (with your choice of whether lo reduce cash payments or stock option compensation or both) as would result in no portion of the Payment being subject to the Excise Tax. whichever of the foregoing amounts, taking into account the applicable federal, state and local employment taxes, income taxes and the Excise Tax results in your receipt, on an after-tax. basis, of the greater amount of the Payment notwid1st-anding that all or some portion of the Payment may be subject to the Excise Tax..

Definitions

Separation from Service. For purposes of this letter, "Separation from Service" means a "separation from service" within the meaning of Section 409A of the Code. Each installment payment provided under this letter shall at all times be considered a separate and distinct payment for purposes of Section 409Aof the Code. Notwithstanding anything in this letter to the contrary, to the extent required to avoid a prohibited distribution under Section 409A of the Code, the benefits provided under this letter will not be provided to you until the earlier of (a) the expiration of the six-month period measured from the date of your Separation from Service with the Company or (b) the date of your death. Upon the first business day after expiration of the relevant period, all payments delayed pursuant to the preceding sentence will be paid iii a lump sum and any remaining payments due will be paid as otherwise provided herein.

Cause. '·Cause " shall mean the occurrence of any of the following events by the individual: (i) commission of any crime involving the Company, or any crime involving fraud, breach of trust, or physical or emotional harm to any person, moral turpitude or dishonesty; (ii) any unauthorized use or disclosure of the Company's proprietary information (other than any such use or disclosure that is not intentional and is not material); (iii) any intentional misconduct or gross negligence that has a material adverse effect on the Company's business or reputation; (iv) any material breach by you of any agreement between you and the Company that is not cured within thirty (30) days after receipt of written notice from the Company describing any such breach; or (v) repeated and willful failure to perform the duties, functions and responsibilities of the individual's position after a written warning from the Company.

Good Reason. " Good Reason" shall mean your resignation from all positions you then hold with the Company if: (A) without your written consent (i) there is a material diminution in the nature or scope of your responsibilities, duties, authority, or tide; (ii) there is a material reduction of your base salary; provided, however, that a material reduction in your base salary pursuant to a salary reduction program affecting all or substantially all of the employees of the Company and that does not adversely affect you to a greater extent than other similarly situated employees shall not constitute Good Reason; or (iii) you are required to relocate your primary work location to a facility or location that would increase your one way commute distance by more than thirty-five (35) miles from your primary work location as of immediately prior to such change, (B) you provide written notice outlining such conditions, acts or omissions to the Company's Chief Executive Officer, President, or General Counsel within thirty (30) days immediately following such material change or reduction, (C) such material change or reduction is not remedied by the Company within thirty (30) days following the Company's receipt of such written notice and (D) your resignation is effective not later than thirty (30) days after the expiration of such thirty (30) day cure period. "Good Reason" shall also mean your resignation, at your sole discretion, on the one-year anniversary of a Change of Control from all positions you then hold with the Company or its successor if by that date you have not entered into a written letter or agreement with the Company or such successor that provides for your continued employment with the Company or such successor. For purposes of clarification, any Qualifying Termination that occurs on the first anniversary of a Change of Control shall be deemed and treated as occurring within the twelve (12) months immediately following a Change of Control for all purposes of this letter.

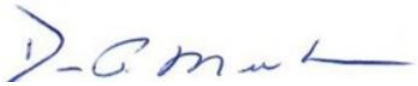
I**nvention, Non-Disclosure, Non-Competition and Non-Solicitation Obligations.** At or prior to the Start Date, you shall execute and deliver for the benefit of the Company the Employee Confident1ality, Assignment of Inventions, Non-Competition and Non-Solicitation Agreement in the form attached hereto as Exhibit A.

At-Will Employment. This letter shall not be construed as an agreement, either express or implied, to employ you for any stated term, and shall in no way alter the Company's policy of

employment at-Will. Similarly, nothing in this letter shall be construed as an agreement, either express or implied, to pay you any compensation or grant you any benefit beyond the end of your employment with the Company except as otherwise explicitly set forth in this letter This letter supersedes all prior understandings whether written or oral, with respect to the subject matter of this letter.

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

Jennifer, I look forward to working with you as part of the Rhythm team. Please indicate your acceptance of this letter of employment by signing a copy of this offer letter and returning it to us by Tuesday, September 29, 2020.



Sincerely,

David Meeker
President & Chief Executive Officer

The foregoing correctly sets forth the terms of my at-will employment with Rhythm. I am not relying on any representations other than those set forth above.

Jennifer Chien Date: September 27, 2020

EXHIBITA
EXECUTED NDA

[See *al/ached]*

Exhibit 21.1

Subsidiaries of Rhythm Pharmaceuticals, Inc.

Entity	Jurisdiction of Organization or Incorporation
Rhythm Pharmaceuticals Limited	Ireland
Rhythm Securities Corp.	Massachusetts

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

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

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

(2) Registration Statement (Form S-8 No. 333-236829) pertaining to the 2017 Equity Incentive Plan and the 2017 Employee Stock Purchase Plan of Rhythm Pharmaceuticals, Inc.,

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

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

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

of our reports dated March 1, 2021, with respect to the consolidated financial statements of Rhythm Pharmaceuticals, Inc. and the effectiveness of internal control over financial reporting of Rhythm Pharmaceuticals, Inc. included in this Annual Report (Form 10-K) of Rhythm Pharmaceuticals, Inc. for the year ended December 31, 2020.

/s/ Ernst & Young LLP

Boston, Massachusetts
March 1, 2021

Exhibit 31.1

CERTIFICATION

I, David P. Meeker M.D., certify that:

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

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

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

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

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

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

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

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

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

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

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

Date: March 1, 2021

/s/ David P. Meeker M.D.
Name: David P. Meeker M.D.
Title: Chief Executive Officer and President
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION

I, Hunter C. Smith, certify that:

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

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

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

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

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

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

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

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

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

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

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

Date: March 1, 2021

/s/ Hunter C. Smith
Name: Hunter C. Smith
Title: Chief Financial Officer
(Principal Financial And Accounting Officer)

Exhibit 32.1

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

I, David P. Meeker M.D., certify pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to my knowledge, this Annual Report on Form 10-K of Rhythm Pharmaceuticals, Inc. for the fiscal year ended December 31, 2020 fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934 and the information contained in such Form 10-K fairly presents, in all material respects, the financial condition and results of operations of Rhythm Pharmaceuticals, Inc.

/s/ David P. Meeker M.D.
Name: David P. Meeker M.D.
Title: Chief Executive Officer and President
(Principal Executive Officer)

March 1, 2021

Exhibit 32.2

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

I, Hunter C. Smith, certify pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to my knowledge, this Annual Report on Form 10-K of Rhythm Pharmaceuticals, Inc. for the fiscal year ended December 31, 2020 fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934 and the information contained in such Form 10-K fairly presents, in all material respects, the financial condition and results of operations of Rhythm Pharmaceuticals Inc.

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

March 1, 2021