Table of Contents

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, 2021
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 $884.4 million, based on the closing price of the registrant's Common Stock on June 30, 2021, 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 50,329,713 shares of the registrant's Common Stock outstanding as of February 22, 2022.

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, 2021. 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, 2021

Table of Contents

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 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 significant 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 sufficient 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 global, 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 hyperphagia, a pathological and insatiable hunger. While obesity affects hundreds of millions of people worldwide, we are advancing IMCIVREE™ (setmelanotide) as a precision medicine strategy for a subset of individuals who have severe obesity due to genetic variants that impair the melanocortin-4 receptor (MC4R) pathway, a pathway in the brain that is responsible for regulating hunger, caloric intake and energy expenditure, which consequently affect body weight. IMCIVREE, an MC4R agonist for which we hold worldwide rights, is the first-ever therapy developed for patients with certain ultra-rare genetic diseases of obesity that is approved or authorized in the United States, European Union (EU) or Great Britain. We made IMCIVREE commercially available in the United States for patients 6 years and older with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency in early 2021, and we are working to achieve market access in several European countries in 2022. In addition to initial commercial efforts, we are preparing to bring IMCIVREE to additional populations in 2022 and beyond. We are advancing a broad clinical development program for setmelanotide in patients with additional rare genetic diseases of obesity 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.

IMCIVREE was approved in November 2020 by the U.S. Food and Drug Administration (FDA) 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. The European Commission (EC) and Great Britain's Medicines & Healthcare Products Regulatory Agency (MHRA), in July and September 2021, respectively, granted marketing authorization to IMCIVREE for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. These approvals were based on Phase 3 data demonstrating a statistically significant and clinically meaningful reduction of weight and hunger in patients 12 years old or older with severe obesity due to POMC, PCSK1 or LEPR deficiency. In addition to the United States and Europe/UK, we and our partners are seeking approval for IMCIVREE to treat patients with these genetic obesities in Israel, China, Hong Kong and Macau.

Additionally, we are seeking regulatory approvals in the United States and Europe for setmelanotide to treat obesity and control hunger in patients with Bardet-Biedl syndrome (BBS) or Alström syndrome. In November 2021, we announced the U.S. FDA has accepted for filing our supplemental New Drug Application (sNDA) for setmelanotide seeking to expand the approved label to include patients with BBS or Alström syndrome, granted us priority review for this sNDA and assigned a Prescription Drug User Fee Act (PDUFA) goal date of June 16, 2022. In October 2021, we announced that we submitted a Type II variation application to the European Medicines Agency (EMA) for setmelanotide for the treatment of obesity and control of hunger in adult and pediatric patients 6 years of age and older with BBS or Alström syndrome. These regulatory submissions are based on positive results from a pivotal Phase 3 clinical trial that

met its primary and all key secondary endpoints and achieved clinically meaningful and statistically significant reductions in body weight and in hyperphagia associated with these syndromes. The submissions include a series of comprehensive individual patient narratives supporting the disease burden of BBS. Our belief that setmelanotide, if approved, has the potential to offer the first therapeutic option for the early-onset, severe obesity and unrelenting hunger that characterize these syndromes. Recently, we have decided to withdraw the Alström syndrome indication from the pending Type II variation application based on feedback from the EMA.

We also are advancing a broad clinical development program evaluating setmelanotide in several ongoing and planned clinical trials, and we are leveraging what we believe is the largest known DNA database focused on obesity - with approximately 45,000 sequencing samples as of December 31, 2021 - to improve the understanding, diagnosis and care of people living with severe obesity due to certain variants in genes associated with the MC4R pathway. Having achieved proof-of-concept in our ongoing exploratory Phase 2 Basket Study evaluating setmelanotide in patients with severe obesity driven by variants in several different MC4R pathway associated genes, we expect to initiate in the first half of 2022, the pivotal Phase 3 EMANATE clinical trial, a randomized, double-blind, placebo-controlled trial to evaluate setmelanotide in five independent sub-studies in patients with obesity due to a heterozygous variant of the POMC/PCSK1 genes or LEPR gene, certain rare variants of the SRC1 gene or the SH2B1 gene, or the N221D variant in the PCSK1 gene. We also have initiated the Phase 2 DAYBREAK clinical trial designed to evaluate setmelanotide in patients who carry a confirmed variant in one or more of 31 additional genes with strong or very strong relevance to the MC4R pathway. Our broad clinical program evaluating setmelanotide in rare diseases of obesity also includes the ongoing exploratory Phase 2 Basket study, an ongoing Phase 2 study evaluating setmelanotide in patients with hypothalamic obesity, a Phase 3 study in pediatric patients with MC4R pathway deficiencies between the ages of 2 and 6 years old, and potential registration-enabling study with our once-weekly formulation of setmelanotide.

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 for MC4R pathway-related obesities. 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 variant in one of 36 genes (or more) related to the MC4R pathway. If these individuals test positive for such a genetic variant, they would be eligible for access to IMCIVREE or enrollment in a clinical trial evaluating setmelanotide. In clinical trials across several different genetic deficiencies, we have seen patients respond to this precision treatment with rapid weight loss of 5 % or more in 12 to 16 weeks. Based on our experience treating more than 100 patients in our Phase 2 and Phase 3 clinical studies, patients who achieve at least 5 % weight loss at approximately 12 to 16 weeks on setmelanotide therapy tend to achieve 10 % weight loss or more within a year, hence these patients demonstrate a robust clinically meaningful response to treatment.

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 biallelic POMC, PCSK1 or LEPR deficiencies, and BBS and Alström syndrome. Based on internal sequencing data, we believe the established epidemiology estimates for BBS ultimately may prove to underestimate the number of people with this syndrome. The epidemiology estimates for the indications being studied in our Phase 3 EMANATE trial suggest that between 100,000 to 200,000 U.S. patients with one of these genetically driven obesities have the potential to respond to setmelanotide. Despite the combined potential addressable patient population likely being larger than rare populations of each individual genetic disorder, these patients face similar challenges as other patients with rare diseases, namely lack of awareness, resources, tests, tools and especially therapeutic options.

We are working to expand access to IMCIVREE globally, beginning with obesities from POMC, PCSK1 and LEPR deficiencies, as we advance towards regulatory approvals in BBS and potentially Alström syndrome and 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 multiple teams 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, as well as additional educational and awareness events directed towards patients and their families and health care providers. And our sequencing efforts, now primarily focused

on our Uncovering Rare Obesity™ (URO) sponsored genetic testing program, fuel MC4R pathway research, disease education and awareness and patient finding.

With approximately 140 employees in the United States and Europe as of January 31, 2022, a rapidly expanding network of key opinion leaders, and an increasing number of treated patients, we are focused on changing the paradigm for the treatment of rare genetic diseases of obesity. Our focused disease awareness and patient finding efforts fuel the key elements of our strategy, including:

- **Rapidly advance development of setmelanotide to reach as many patients as possible:** We are focused on expanding access to setmelanotide in the United States, Europe, Great Britain and select other markets for our initial indications and preparing for a successful U.S. launch of setmelanotide for BBS and potentially Alström syndrome, pending FDA approval by the June 2022 PDUFA date. Additionally, we are executing on the clinical trials which, if successful, potentially will enable registration of setmelanotide in an expanding number of indications. With multiple Phase 2 and 3 trials, we anticipate bringing approximately 100 clinical trials sites in the United States, Europe, Middle East and China. 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 awareness and communications efforts geographically to support genetic testing around trial sites in order to build these local referral networks to support trial recruitment and enrollment.

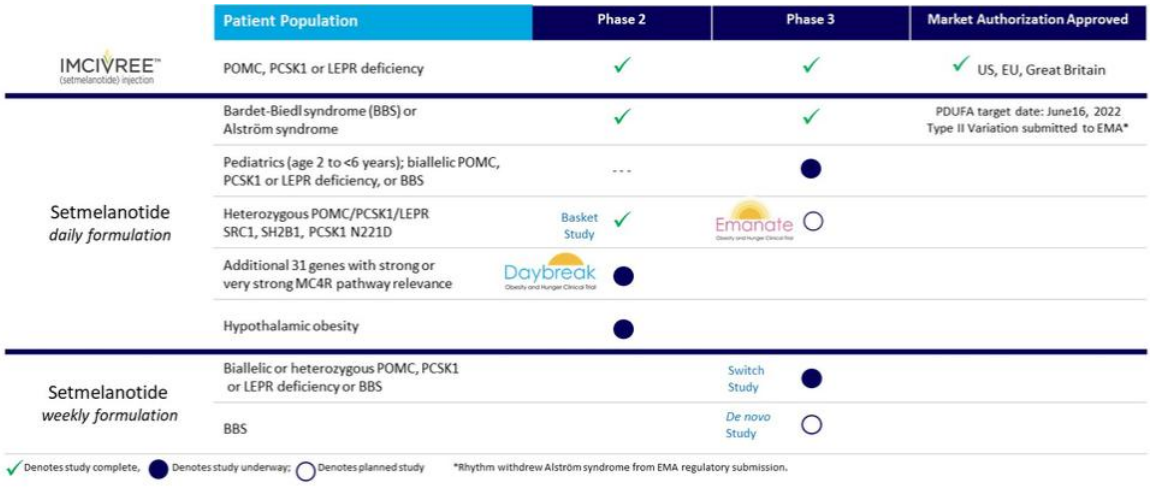
- **Ensure global access to IMCIVREE:** We are actively pursuing a global strategy for our clinical development, commercial and community building programs. In 2021, we laid the foundation for an emerging global organization focused on North America and major markets in Europe. We have established initial partnerships in Asia and the Middle East, and we are actively exploring opportunities to provide setmelanotide to patients in South America.

- **Leverage genetic testing programs to support clinical trial enrollment and commercial launch activities:** We are committed to expanding our obesity DNA database by expanding access and availability to genetic testing for individuals with early-onset, severe obesity and hyperphagia. Approximately 50% of patients with early-onset severe obesity test positive for a variant in one of 36 MC4R pathway genes which we are studying in our phase 2 and 3 trials. 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 individuals with obesity over the next few 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 also are focused on developing and bringing follow-on product candidates to market, including a weekly formulation of setmelanotide as well as an auto-injector, designed to be more convenient and patient-friendly. Additionally, we have initiated a clinical trial in pediatric patients from 2 years to younger than 6 years of age with obesity due to POMC, PCSK1 or LEPR deficiency, or BBS, as we know early-onset obesity manifests in this young age group. We also are exploring more selective and more potent MC4R agonists through preclinical development of our library of MC4R agonist candidates.

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:



Market Overview

Early-onset, Severe Obesity, Hyperphagia, 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, a pathological, overwhelming, obsessive, and relentless hunger that drives a severe preoccupation with food and extreme food-seeking behaviors. Lifestyle interventions are not therapeutic in patients with rare genetic diseases of obesity, because they fail to address the underlying genetic impairment of central energy regulation.

Accordingly, the discovery that the MC4R pathway regulates both energy intake (hunger) and energy expenditure to balance food intake and caloric expenditure has made it 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 variants affecting the MC4R pathway, including BBS, Alström syndrome, certain variants of the POMC, PCSK1, LEPR, SRC1 and SH2B1 genes, as well as MC4R deficiency obesity and deficiencies in upwards of 31 additional genes with strong or very strong relevance to the MC4R pathway. With a deeper understanding of this critical signaling pathway, we are taking a different approach to drug development by focusing on specific genetic variants affecting the MC4R pathway. We believe that this approach has the potential to provide dramatic improvements in obesity and hyperphagia by restoring lost function in the MC4R pathway.

Obesity Caused by Rare Genetic Variants Affecting the MC4R Pathway

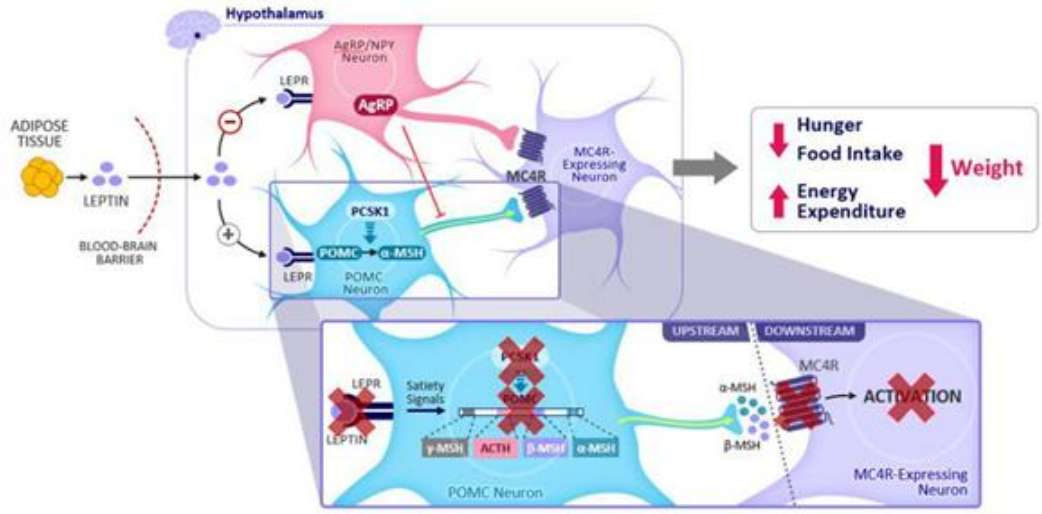
The MC4R pathway, which has been the focus of extensive scientific investigation for many years, regulates hunger, caloric intake, and energy expenditure, which consequently affect body weight. The critical role of the MC4R pathway in weight regulation is supported by the observation that single gene variants 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 adiposity and satiety signals, including those resulting from the hormone leptin acting through the 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 variants disrupt this pathway, it can lead to insufficient MC4R activation and downstream signaling; the result of which is hyperphagia and severe obesity.

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

Setmelanotide Development Targets: Upstream Deficiencies Affecting the MC4R Pathway



AgRP, agouti-related protein; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; ACTH, adrenocorticotropic hormone; PCSK1, proprotein convertase subtilisin/kexin-type 1; POMC, proopiomelanocortin; . Reference: Yazdi FT et al. PeerJ. 2015;3:e856.

We are focused on developing setmelanotide for genetic disorders that arise due to variants in this pathway that are upstream of the MC4R. With our expanding clinical development program, we are evaluating setmelanotide in Phase 2 and 3 trials for the treatment of obesity due to variants 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-expressing neuron downstream of the genetic impairment. In this way, we believe setmelanotide acts as restorative therapy, to restore lost signaling of the MC4R pathway.

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 hyperphagia. Of the tens of millions of individuals with obesity in the United States, the U.S. Center for Disease Control (CDC) estimates that there are approximately 5 million individuals whose severe obesity had early onset between the ages of 2 and 5 years old. The table below summarizes, using the estimations described below, the indications currently approved or under active clinical investigation.

Approved by the U.S. FDA and authorized by the EC and Great Britain's MHRA[1]	
Obesity due to biallelic POMC or PCSK1 deficiency	~100 – 500 U.S. patients
Obesity due to biallelic LEPR deficiency	~500 – 2,000 U.S. patients

Under review by U.S. FDA with PDUFA target date of June 16, 2022, and under review by EU EMA	
Bardet-Biedl syndrome	~1,500 – 2,500 U.S. patients
Alström syndrome	~500 U.S. patients

Setmelanotide currently being evaluated in Phase 2 or Phase 3 trials	
Heterozygous POMC or PCSK1 variants	~45,000 U.S. patients
Heterozygous LEPR variants	~25,000 U.S. patients
SRC1 variants	~20,000 U.S. patients
SH2B1 variants	~23,000 U.S. patients
PCSK1 N221D variant	~100,000 U.S. patients
MC4R variants	~10,000 U.S. patients*
Hypothalamic obesity	>4,500 U.S. patients**

1. Approved for use in patients six years of age and older.
These calculations rely on internal and proprietary sequencing data and current estimated responder rates to setmelanotide therapy, and they 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; ** Internal Company estimate is based on reported incidence of hypothalamic obesity following craniophryngioma and long-term survival rates, Zacharia, et al., *Neuro-Oncology* 14(8):1070–1078, 2012. doi:10.1093/neuonc/nos142; and Muller, et al., *Neuro-Oncology* 17(7), 1029–1038, 2015 doi:10.1093/neuonc/nov044.

We believe that the patient populations in Europe 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 European countries and these estimates are therefore based solely on applying relative population percentages to the Rhythm-derived estimates described above.

Prevalence estimates for Bardet-Biedl syndrome vary markedly between populations, from 1 in 160,000 in northern European populations with higher prevalence rates in some additional regions throughout the world. Our estimate is that the number of patients with BBS in the United States is between 1,500 to 2,500 people and that it is a slightly higher number in Europe. We believe the BBS community in EU member states and Great Britain is particularly well established and more advanced than in the United States, as we believe there are approximately 1,500 patients diagnosed and being cared for at academic centers in Europe. Additionally, our genetic sequencing data support our belief that these prevalence estimates may be lower than the actual disease prevalence.

For patients with genetic variants of the MC4R pathway, 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 2021 based on sequencing data from approximately 45,000 individuals with obesity, 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

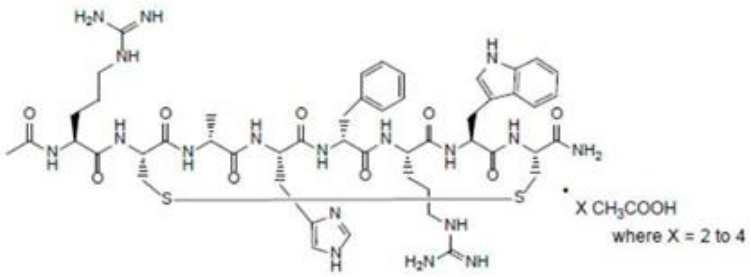
Although drugs approved for general obesity potentially can be used in patients with obesity and MC4R pathway variants, all currently available products have limited efficacy and treat symptoms without addressing the underlying biology of MC4R impairment. For example, drugs which delay gastric emptying 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 variants, these therapies also do not specifically address the impaired signaling in this central energy regulating pathway. Similarly, bariatric surgery which has been shown to be quite effective in the general population with obesity, may be unsuccessful in patients with MC4R variants for the same reason.

IMCIVREE™ (setmelanotide)

IMCIVREE was approved in November 2020 by the U.S. FDA 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, and in July and September 2021, respectively, by the EC and Great Britain's MHRA for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. These approvals were based on Phase 3 data demonstrating a statistically significant and clinically meaningful reductions in weight and hunger in patients 12 years old or older with severe obesity due to POMC, PCSK1 or LEPR deficiency. As an MC4 receptor agonist, IMCIVREE is designed to restore impaired MC4 receptor pathway activity arising due to genetic impairments upstream of the MC4 receptor.

IMCIVREE contains setmelanotide acetate, a melanocortin 4 receptor (MC4R) 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 hyperphagia, an extreme, insatiable hunger, beginning at a young age and 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 biallelic genetic variants is deficiency 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 other hormonal deficiencies, such as hypoadrenalism, as well as other characteristics of MSH deficiency such 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 above the normal weight growth curves. These patients and their caregivers often attempt to stabilize body weight with the help of psychologists, nutritionists and pediatric endocrinologists, all without significant success, since none of these interventions addresses the underlying biology of the impact of the POMC/PSCK1 deficiency on the MC4R pathway.

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 people with severe obesity and biallelic mutations that impair the activity of leptin, including disruption of signaling at the LEPR, known as LEPR deficiency obesity. Under normal conditions, leptin is released from adipose (fat) tissue as a signal of the body's energy reserves, and can activate POMC neurons and the downstream MC4R to signal for decreased energy intake and increased energy expenditure. However, like other deficiencies upstream in the MC4R pathway, lack of signaling at LEPR results in loss of function in the MC4R pathway and loss of signaling of downstream MC4R expressing neurons, resulting in hyperphagia and early-onset severe obesity.

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% were adults and 38% were aged 16 years or younger. In Study 1, 50% of patients were female, 70% were White, and the median baseline BMI was 40.0 kg/m^2 (range: 26.6-53.3). In Study 2, 73% of patients were female, 91% were White, and the median baseline BMI was 46.6 kg/ m^2 (range: 35.8-64.6).

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

Development of Setmelanotide for Additional Indications

Bardet-Biedl and Alström syndromes

Bardet-Biedl syndrome (BBS) is a life-threatening, ultra-rare orphan disease. BBS is a disease that causes hyperphagia and severe obesity beginning in early childhood, as well as vision loss, polydactyly, kidney abnormalities, and other signs and symptoms. For patients with BBS, 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, including in the MC4R pathway, 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 variants that result in a similar syndrome of clinical manifestations. Recent scientific studies identify deficiencies affecting the MC4R pathway as a potential cause of the hyperphagia and obesity associated with BBS, and demonstrate that an MC4R agonist can directly impact these symptoms. Currently there are no approved or effective therapies for BBS.

Alström syndrome is a life-threatening, ultra-rare orphan disease. It is a monogenic disorder that causes hyperphagia and obesity beginning in early childhood, 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 hyperphagia and obesity, 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 hyperphagia and obesity associated with Alström syndrome. While Alström syndrome is less well studied than BBS, the similar pathophysiology of cilia dysfunction and clinical presentation support our belief that deficiencies in the MC4R pathway are implicated in the hyperphagia and obesity observed in Alström syndrome. Therefore, we hypothesize that setmelanotide treatment can be applied to treat Alström syndrome.

In September 2021, we submitted an sNDA to the FDA for setmelanotide for the treatment of obesity and control of hunger in adult and pediatric patients 6 years of age and older with BBS or Alström syndrome, and in October 2021, we submitted a Type II variation application to the EMA for the same indications and patient populations. These submissions were based on based on data from our pivotal Phase 3 clinical trial of setmelanotide in patients with BBS or Alström syndrome. As we first reported in December 2020, the trial met its primary endpoint and all key secondary endpoints, with statistically significant and clinically meaningful reductions in weight and hunger at 52 weeks on therapy. All patients who met the primary endpoint, defined as at least 10 % weight loss, had BBS and none had Alström syndrome. However, data from this Phase 3 trial are supported by results from the Phase 2 trial, which suggested that treatment with setmelanotide may result in decreased weight and hunger in patients with Alström syndrome. In addition, data from a predefined exploratory endpoint showed that in patients with BBS or Alström syndrome who were younger than 18 years old and likely still growing in height, setmelanotide treatment was associated with clinically meaningful reductions in BMI Z scores. The BMI Z score, or BMI standard deviation score, represents the number of standard deviations from median BMI by child's age and sex, and represents a unit of measure that accounts for height as well as weight in growing children and adolescents. Based on our discussion with the FDA and the EMA, we believe the decision or decisions to approve and/or authorize setmelanotide for BBS and Alström would be made independently, and recently we have decided to withdraw the Alström syndrome indication from the pending Type II variation application based on feedback from the EMA. In November 2021, we announced that the FDA accepted for filing our sNDA with Priority Review and assigned a PDUFA goal date of June 16, 2022 for our sNDA.

Based on the data included in our regulatory applications, we believe setmelanotide has the potential to address the early-onset, severe obesity and hyperphagia that characterize these diseases. In addition to the topline data reported from our Phase 3 trial of setmelanotide in patients with BBS or Alström syndrome, we have also presented several poster and oral presentations featuring the topline data from the pivotal cohort as well as additional updated data also including the supplemental cohort at medical meetings during 2021. Our pivotal, Phase 3 trial that combined both BBS and Alström syndrome was 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 had obesity, defined as BMI equal to or greater than 30 kg/m^2 for patients aged 16 years or older or weight greater than 97th percentile for age and sex on growth chart assessment for patients 6 to 15 years of age. The primary endpoint was the proportion of participants (aged 12 years or older) who achieved at least 10 % reduction in body weight from baseline after 52 weeks of setmelanotide treatment. Key secondary endpoints further assessed changes in body weight and hunger, and daily maximal hunger score was based on participant responses to scoring their "most" hunger during the day using a numerical rating scale ranging from 0 to 10, where 0 is not hungry at all and 10 is the hungriest possible. Recognizing that adolescents normally gain height and weight, an analysis was performed to assess changes in BMI Z scores in participants with BBS who were younger than 18. This trial enrolled 38 participants, of which 32 were confirmed to have BBS and 6 were confirmed to have Alström syndrome. Five study participants who were under 12 years old and two participants who were equal to or more than 12 years old and who discontinued before receiving active therapy were not included in the primary analysis.

In this Phase 3 trial in participants with BBS or Alström syndrome, setmelanotide was associated with significant and clinically meaningful reductions in body weight and hunger, with outcomes driven by responses in individuals with

BBS. Overall, this study met its primary and key secondary efficacy endpoints demonstrating that approximately 52 weeks of treatment with setmelanotide produced:

- A statistically significant proportion of patients who achieved at least 10% reduction in body weight over approximately 52 weeks of treatment;
- Statistically significant and clinically meaningful reductions in mean body weight over approximately 52 weeks of treatment;
- Statistically significant and clinically meaningful reductions in the mean weekly average of the Daily Hunger Questionnaire over approximately 52 weeks of treatment, whether analyzed by most/worst score over 24 hours, average score over 24 hours, or morning hunger score; and
- A statistically significant proportion of patients who achieved an equal to or greater than 25% improvement in the weekly average of the Daily Hunger score over approximately 52 weeks, whether analyzed by most/worst score over 24 hours, average score over 24 hours, or morning hunger score.

In the primary analysis, a total of 28 patients who had BBS were older than 12 years, 15 were adults and 13 were adolescents between the ages of 12 and 18. As presented at The Endocrine Society Annual Meeting in March 2021, data after approximately 52 weeks of treatment with setmelanotide demonstrated:

- Of the 15 adult patients with BBS:
  - there was a -9.1% mean percentage change from baseline in BMI;
  - 46.7%, or seven adults, achieved at least 10% weight reduction from baseline; and
  - 60%, or nine adults, achieved at least 5% weight reduction from baseline;
- Of the 14 patients who were younger than 18 years old:
  - there was a -9.5% mean percentage change from baseline in BMI;
  - 85.7%, or 12 adolescents, had a reduction from baseline in BMI Z of greater than 0.2; and
  - there was a -0.75 point mean change from baseline in BMI Z score.

We also presented the 14-week, placebo-controlled data from this trial at the 59th Annual European Society for Paediatric Endocrinology (ESPE) Meeting in September 2021. Patients with BBS treated with setmelanotide achieved an average BMI reduction of −1.5 kg/m^2 (or a decrease of 3.8%) at Week 14 compared with patients on placebo who had negligible change from baseline ($P<0.05$). Treatment with setmelanotide during that 14-week period also significantly reduced the Daily Hunger Questionnaire's Most/Worst Hunger score compared to placebo in patients in the pivotal cohort aged 12 years or older, with directionally consistent results observed when the analysis was repeated using all patients (from the pivotal and supplemental cohorts).

In November 2021, we presented the first-ever data on the health-related quality of life (HRQOL) and experience of patients with BBS at The Obesity Society's ObesityWeek®. This research was conducted as a post-hoc analysis of data from our Phase 3 study, using the self-reported Pediatric Quality of Life Inventory (PedsQL) or the Impact of Weight on Quality of Life Questionnaire-Lite (IWQOL-Lite), both of which are 100-point scales, with zero being the worst and 100 being the best. Key findings include:

- 85% of patients reported clinically meaningful improvements in their HRQOL status after one year of setmelanotide therapy, or preserved their non-impaired HRQOL status;
- In adult patients, changes in their IWQOL score were clinically meaningful with a mean increase of 12 points after one year on setmelanotide therapy from 74.9 at baseline;

- In pediatric patients, changes in their PedsQL score were clinically meaningful with a mean increase of 11.2 after one year on setmelanotide therapy from 67.2 at baseline;

- For the subset of patients without cognitive impairment, clinically meaningful improvements in outcomes such as body mass index and hunger mirrored their improvements in HRQOL;

- HRQOL improvements were sustained over the 52-week trial period.

On February 16, 2022, we announced positive interim data from our long-term extension study evaluating setmelanotide in patients with BBS. Of the patients enrolled in our long-term extension trial, 19 individuals with BBS had reached 24 months on therapy. As of a data cutoff date of October 29, 2021:

• The mean percent reduction in BMI from pivotal trial baseline was -14.3% (n=19);

• The mean percent reduction in body weight from pivotal trial baseline among patients 18 years of age or older was -14.9% (n=6);

• The mean reduction in BMI Z score from pivotal trial baseline among patients younger than 18 was -0.72 (n=12). For one patient who was 17 years old when enrolled and at baseline in the pivotal trial, BMI Z score could not be calculated as this patient was 20 years old at 24 months on therapy.

Overall, 34 patients with BBS transitioned from our phase 3 pivotal trial into our long-term extension study. We anticipate reporting updated data from this trial at a medical meeting in the spring of 2022. Consistent with prior clinical observations, setmelanotide was generally well-tolerated in the long-term extension study and no new safety signals were observed.

We studied patients with Alström syndrome and severe obesity in two clinical trials, our exploratory Phase 2 Basket study and our pivotal Phase 3 study in conjunction with BBS. 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 of equal to or greater than 10 % weight loss. However, there were signals of potential efficacy in some patients, and based on those signals and data from the Phase 2 Basket study, we believe setmelanotide has the potential to address the unmet medical need in patients with Alström syndrome, hyperphagia and severe obesity.

A total of 12 patients with Alström syndrome entered these trials, with eight of them having been exposed to setmelanotide for at least 26 weeks, and overall patients had setmelanotide exposure up to 79 weeks. As the majority (67%) of patients were less than 18 years of age and still growing in height, we believe changes in BMI Z scores are a more appropriate measure of setmelanotide’s potential effects than change in body weight. Reductions in BMI Z scores were observed in 5 of the 6 patients (or 83%) under the age of 18 years who had at least 26 weeks of exposure to setmelanotide, with robust clinically meaningful reductions greater than 0.3 points observed in 3 of these patients. Clinically meaningful reductions in body weight (equal to or greater than 5%) were observed in 2 of the 8 (or 25%) patients with Alström syndrome with at least 26 weeks on setmelanotide, with one 12-year-old patient losing more than 20% of initial body weight at baseline. With respect to hunger, 4 of the 6 (or 66.7%) patients with evaluable data demonstrated clinically meaningful reductions of 1 to 2 points in hunger, as measured by the most/worst hunger question of the Daily Hunger Questionnaire. Five of the eight patients with Alström syndrome treated for at least 26 weeks decided to continue treatment with setmelanotide in our ongoing extension study.

In addition to positive results from our pivotal Phase 3 clinical trial, we included in our regulatory submissions a series of comprehensive individual patient narratives supporting our belief that setmelanotide, has the potential to address the hyperphagia and early-onset, severe obesity that characterize these syndromes.

Additional MC4R Pathway Genetic Variants

With significant advances in gene sequencing and analysis, we have deepened our understanding of the relationship between genetics and severe obesity. We also are advancing a broad clinical development program evaluating

setmelanotide in several ongoing and planned clinical trials, and we are leveraging the largest known DNA database focused on obesity - with approximately 45,000 sequencing samples as of December 2021 - to improve the understanding, diagnosis and care of people living with severe obesity due to certain variants in genes associated with the MC4R pathway. There remains a significant unmet need with no effective therapeutic options for patients with these rare genetic diseases of obesity, and we believe setmelanotide has the potential to address the hyperphagia and severe obesity associated with these rare genetic diseases.

Having achieved proof-of-concept in our ongoing exploratory Phase 2 Basket Study evaluating setmelanotide in patients with severe obesity driven by variants in several different MC4R pathway associated genes, we expect to initiate in the first half of 2022, the pivotal Phase 3 EMANATE clinical trial to evaluate setmelanotide in five independent sub-studies in patients with variants in one of five specific genes within the MC4R pathway. In addition to EMANATE, we also initiated the Phase 2 DAYBREAK clinical trial to evaluate setmelanotide in patients who carry a confirmed variant in one or more of 31 genes with strong or very strong relevance to the MC4R pathway. Additionally, in our ongoing exploratory Phase 2 Basket Study, we are evaluating setmelanotide in patients with obesity arising due to heterozygote loss of function mutations in the MC4R gene itself. We also have a separate trial evaluating setmelanotide in patients with hypothalamic obesity, or HO, a severe obesity that arises after injury to the hypothalamus (such as from a tumor or the treatment of a tumor in this location). We anticipate reporting data from both of these Phase 2 studies in the first half of 2022.

Phase 3 EMANATE Trial

In the first half of 2022, we expect to initiate our pivotal Phase 3 EMANATE clinical trial, a randomized, double-blind, placebo-controlled trial, designed to evaluate setmelanotide in five independent sub-studies in patients with obesity due to: a heterozygous variant of the POMC/PCSK1 genes or LEPR gene, certain variants of the SRC1 gene or the SH2B1 gene, or PCSK1 N221D deletions within the MC4R pathway. The epidemiology estimates for the indications being studied in our Phase 3 EMANATE trial suggest that between 100,000 to 200,000 U.S. patients with one of these genetic deficiencies have the potential to respond to setmelanotide.

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. Obesity due to rare variants in the SRC1 gene is an autosomal dominant disorder that is characterized by early-onset severe obesity and hyperphagia, as SRC1 variants found in individuals with severe obesity significantly impaired leptin-induced POMC expression (Yang et al 2019, Nat Comm. 10, Article 1718). Specifically, SRC1 is a transcriptional coactivator that has links to both the leptin receptor and to POMC. When the leptin receptor is activated, SRC1 is activated through a cascade of events that then drives the expression of POMC. Individuals who have heterozygous loss-of-function variants in their SRC1 genes can have insufficient leptin receptor activation of the MC4R pathway as a result of decreased POMC expression. This decreases the amount of available MSH to activate the MC4R, consequently resulting in hyperphagia and obesity in these individuals. Obesity due to variants in the SHWB1 gene is a rare genetic disease that is characterized by early-onset severe obesity, hyperphagia, hyperinsulinemia, and reduced final height. SH2B1 variants 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 exploratory Phase 2 Basket Study

In January 2021, we announced proof-of-concept data from our exploratory Phase 2 Basket Study in multiple patient cohorts of patients with severe obesity due to a variant in one of the two alleles in the POMC, PCSK1, or LEPR genes (PPL HET obesity), as well as the SRC1 and SH2B1 genes. We provided subsequently furnished updated data in multiple presentations at medical meetings throughout 2021. The ongoing Phase 2 Basket Study is an open label study designed to evaluate setmelanotide in patients with obesity defined as Body Mass Index (BMI) $\geq$ 30 kg/m^2 for patients 16

years of age or older or BMI≥ 95th percentile for age and gender for patients between 6 and 16 years old. Patients were stratified by cohort according to their genetic variant. The primary endpoint of the study is the percent of patients in each subgroup showing at least a 5% loss of body weight over three months ("clinical responders").

PPL HET Obesity (POMC, LEPR, PCSK1) highlights included:

- Overall, 12 of 35 patients (34.3%) achieved the primary endpoint. This full analysis includes six patients who withdrew early;
- Mean reduction from baseline in body weight over three months across all 35 patients was -3.7%, 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 over three months was -10.1%.

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 on 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 are 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 PPL 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%) with a pathogenic or likely pathogenic variant achieved greater than 5% weight loss over three months;
- Four of eight patients (50.0%) with the N221D variant of the PCSK1 gene achieved greater than 5% weight loss over three months; and
- Four of 19 patients (21.1%) with a variant of unknown significance (VUS) achieved greater than 5% weight loss over three months.

In September 2021, we presented updated interim data from the SRC1 and SH2B1 cohorts at the at the 59th Annual European Society for Paediatric Endocrinology (ESPE) Meeting. The data presented were based on an interim analysis of patients who completed 12 weeks of therapy. These presentations included analyses that showed setmelanotide achieved clinically meaningful weight loss or BMI Z reduction in 30% (9 of 30) of study participants with obesity due to variants of the SRC1 gene and clinically meaningful weight loss or BMI Z reduction in 43% (15 of 35) of study participants with obesity due to variants of the SH2B1 gene, including 16p11.2 chromosomal deletions.

Specifically in the SRC1 cohort, a total of 30 patients with obesity and deficiency in the SRC1 gene were enrolled in the full analysis set of this study. These patients had a mean BMI of 45.4 kg/m^2 or BMI Z of 3.0 at baseline. Highlights of these data, as of a cut-off date of March 16, 2021, include:

- Nine of 30 (or 30%) of patients achieved a clinically meaningful response to setmelanotide at three months, as defined by weight loss of 5% or greater from baseline, or for patients under 18 years old, a reduction of at least 0.15 in BMI Z score:
    - In adult patients 18 years or older, six of 20 (or 30%) achieved 5% or greater weight loss at three months;

- In patients younger than 18 years, three of 10 (or 30%) achieved a BMI Z reduction of 0.15% or more at three months.

- Across all enrolled patients, the mean overall weight loss from baseline to three months among patients 18 years and older (a sample of 20) was -4.0% (a standard deviation of 3.3%), and the mean overall BMI Z score reduction from baseline to three months among patients younger than 18 years (n=10) was -0.21 (a standard deviation of 0.23).

In addition, these interim data showed a clear separation between patients who responded to setmelanotide treatment at three months and those who did not:

- The mean body weight reduction for adult patients who responded (n= 6) was 7.9% (90% confidence interval (CI), −9.7 to −6.0), as compared to 2.3% (90% CI, −3.2 to −1.4) for adult patients who did not respond (a sample of 14);

- The mean BMI Z reduction for patients younger than 18 years who responded (n= 3) was 0.48 (90% CI, −0.95 to −0.01), as compared to 0.09 (90% CI, −0.11 to −0.07) for those who did not respond (n= 7).

In the SH2B1 cohort, a total of 35 patients with obesity and 16p11.2 deletions that include the SH2B1 gene or deficiency in the SH2B1 gene were enrolled in the full analysis set of this study. These patients had a mean BMI of 47.2 kg/m^2 or BMI Z of 3.6 at baseline. Highlights of these interim data, as of a cut-off date of March 16, 2021, include:

- Fifteen of 35 (or 42.9%) of patients achieved a clinically meaningful response to setmelanotide at three months, as defined by weight loss of 5% or greater from baseline, or for patients under 18 years old, a reduction of at least 0.15 in BMI Z score:

  - In patients 18 or older, eight of 22 (or 36.4%) achieved 5% or greater weight loss at three months;
  - In patients younger than 18 years, seven of 13 (or 53.8%) achieved a BMI Z reduction of 0.15% or more at three months.

Across all enrolled patients, the mean overall weight loss from baseline to three months among patients 18 years and older (n= 22) was -3.1% (a standard deviation of 3.9%), and the mean overall BMI Z score reduction from baseline to three months among patients younger than 18 years (n= 13) was -0.15 (a standard deviation of 0.13). In addition, the interim data showed a clear separation between patients who responded to setmelanotide treatment at three months and those who did not:

- The mean body weight reduction for adult patients who responded (n= 8) was 7.2% (90% CI, −8.6 to −5.8), as compared to 0.8% (90% CI, −1.9 to 0.3) for adult patients who did not respond (n= 14);

- The mean BMI Z reduction for patients younger than 18 years who responded (n= 7) was 0.25 (90% CI, −0.29 to −0.21), as compared to 0.03 (90% CI, −0.08 to 0.02) patients younger than 18 years who did not respond (n= 7).

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.

MC4 Receptor Deficiency Obesity

In the first half of 2022, we anticipate reporting interim data from ongoing exploratory Phase 2 Basket Study 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 early-onset severe 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 we believe can be rescued by setmelanotide (e.g. may not responsive to the endogenous ligand MSH, but would otherwise respond normally to setmelanotide).

Hypothalamic Obesity

Hypothalamic obesity, or HO, is a severe obesity that arises from mechanical hypothalamic injury. 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/or 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.

As of February 1, 2022, we have completed enrollment in our Phase 2, multi-center, open-label, proof-of-concept study designed to assess the effect of setmelanotide over 16 weeks on weight-related assessments in patients aged 6 to 28 years who are affected by HO. We enrolled more than 15 subjects across 3-5 clinical sites in the United States. The primary endpoint is the percentage of subjects aged >12 years with ≥5 % body weight loss from baseline to week 16, compared to a historic control of <5 % in this subject population. All enrolled patients will have obesity, 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.

We anticipate announcing results from a preliminary data analysis from this trial in the first half of 2022.

Weekly Formulation of Setmelanotide

In collaboration with Camurus AB, or Camurus, we have developed a once-weekly, long-acting formulation of setmelanotide using FluidCrystal® technology. When injected subcutaneously, aqueous body fluid may be absorbed by the excipient lipid phase, which may then form 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 October 2021, we presented full data from our trial that evaluated the weekly formulation of setmelanotide in patients with obesity at the Obesity Medicine Association's (OMA) Overcoming Obesity 2021 Conference. The data showed that otherwise healthy people with obesity treated with the weekly formulation of setmelanotide (QW) achieved comparable weight loss to those treated with the daily formulation, and that both weekly and daily formulations of setmelanotide (QD) were observed to be generally well tolerated. A total of 82 individuals aged 18 to 55 years with body mass index (BMI) ≥35 kg/m^2 were included in the data analysis. Based on the data from the study, we concluded the safety profile of QW setmelanotide was similar to that of the QD formulation; in healthy volunteers, peak and trough QW setmelanotide concentrations were generally consistent with the concentrations of the QD formulation; and weight and hunger change at Week 12 was comparable between QW and QD setmelanotide. Notably, the weight and hunger score changes in otherwise healthy individuals with obesity receiving both formulations were lower than those reported separately in patients with rare genetic diseases of obesity associated with an impaired MC4R pathway who received setmelanotide. 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.

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. Of the 249 reported injection site reactions, 247 (≥99%) were classified as mild.

In December 2021, we initiated a Phase 3 trial to evaluate the weekly formulation of setmelanotide in patients with rare genetic diseases of obesity. The weekly switch trial is a randomized, double-blind switch trial in patients with obesity due to biallelic or heterozygous POMC, PCSK1 or LEPR deficiency or a clinical diagnosis of BBS with genetic confirmation, who were previously enrolled in our long-term, open-label extension trial. We expect to enroll 30 patients, randomized 1:1 to receive once-weekly setmelanotide and once-daily placebo, or once-daily setmelanotide and once-weekly placebo for 13 weeks. Following the 13-week randomized treatment period, patients will crossover to an open-label, 13-week study in which all patients will receive once-weekly setmelanotide. The primary efficacy endpoint is a responder analysis, based on the proportion of patients with no weight gain defined as a change of 5 % or less from baseline to week 13.

In addition, we plan to initiate a second trial to evaluate the weekly formulation of setmelanotide in the second half of 2022. This *de novo* trial will be a randomized, double-blind Phase 3 clinical trial in patients with BBS who live outside the United States. We expect to enroll 40 patients, randomized 1:1 to receive 30 mg of setmelanotide or placebo once weekly for 18 weeks. Following the 18-week treatment period, patients will continue on treatment, or crossover from placebo to active therapy, for an additional 14 weeks. The primary efficacy endpoint is the mean change from baseline in body weight after approximately 18 weeks of once weekly dosing.

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 adverse events, or 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.

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 approximately half of the 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. 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 United States and authorized in the EU and Great Britain for patients 6 years of age and older. Rare genetic diseases of obesity often present early in life, and we have identified children with genetic obesity under 6 years of age who we believe may potentially benefit from treatment with setmelanotide. In the first quarter of 2022, we announced initiation of the Phase 3 trial evaluating daily setmelanotide in pediatric patients who are between the ages of 2 and 6 years old. The trial is a multi-center, one-year, open-label Phase 3 trial in pediatric patients with obesity due to biallelic POMC, PCSK1 or LEPR deficiency or a clinical diagnosis of BBS with genetic confirmation. The primary efficacy endpoint is a responder analysis, based on the proportion of patients who experience a decrease from baseline over one year in BMI Z of ≥0.2. In addition, we have initiated discussions with the EMA to modify our EMA-approved Pediatric Investigation Plan (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 have initiated a program to identify next generation MC4R agonists based on the setmelanotide chemical space that we believe will 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 an 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 45,000 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. Our sequencing data has come from four distinct sources in recent years: the Genetic Obesity ID | Genotyping Study, a global network of collaborations with obesity researchers with individual sample collections, institutional biobanks and Uncovering Rare Obesity or URO. 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.

Uncovering Rare Obesity

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. 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, 2021, 2,758 United States health care providers have requested 28,171 Uncovering Rare Obesity kits, and 13,029 sequencing tests have been ordered and patient samples collected.

This program complements several initiatives designed to advance the understanding of genetic causes of severe obesity, and Uncovering Rare Obesity broadens these efforts and brings access to genetic testing into the community setting. Currently available physician-ordered genetic testing panels are often cost prohibitive, while many consumer genetic tests are incomplete when it comes to genetic disorders of obesity. This makes it difficult to confirm an underlying

genetic cause of severe obesity. We believe the program marks an important step in the understanding of these disorders that might help patients and their families find new diagnosis and treatment strategies in the years ahead.

Our partner Prevention Genetics, a Clinical Laboratory Improvement Amendments-College of American Pathologists of CLIA/CAP-certified independent laboratory, conducts 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.

Commercial Efforts for IMCIVREE

We are focused on making IMCIVREE available globally. In the United States, we have executed on our strategy of making IMCIVREE commercially available to patients with obesity due to POMC, PCSK1 or LEPR deficiency, and we are building out the infrastructure and teams in preparation for a commercial launch for patients with BBS and potentially Alstrom syndrome, if our sNDA is approved by FDA. We expect IMCIVREE will be commercially available in the key European markets, UK and Israel in 2022. 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 variants 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 of 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 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.

We are working with the broader community of physicians, patients and families to improve the path to an accurate diagnosis as we support disease education through our medical and commercial team efforts. Additionally, 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.

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 syndrome 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 population with obesity.

Following marketing authorization by both the European Commission and Great Britain’s MHRA for biallelic POMC, PCSK1 and LEPR deficiency, we are focused on achieving market access and reimbursement for IMCIVREE with country level authorities. As of March 1, 2022:

- The German Federal Joint Committee (G-BA) has unanimously voted to exclude IMCIVREE from its lifestyle exemption list for POMC, PCSK1and LEPR deficiency obesities. In Germany, drugs classified as lifestyle drugs which including those designed to effect weight loss, smoking cessation or hair loss are not eligible for reimbursement. This first-ever exclusion marks an important recognition that IMCIVREE is designed to treat rare genetic diseases that manifest as obesity and that this group of diseases is distinct from general obesity. With this exemption status, IMCIVREE would be eligible for national coverage and reimbursement. We expect first commercial sales in Germany in the second quarter of 2022.

- The French Haute Autorité de Santé (HAS) has granted paid early access for IMCIVREE for patients with POMC, PCSK1 or LEPR deficiency obesity which we expect to commence in the second quarter of 2022.

- We have submitted reimbursement dossiers in seven countries, including France, Germany, Italy, Spain, the Netherlands, Israel, and the United Kingdom, with positive feedback from EU payers and favorable HTA ratings from authorities in several countries.

We have established initial partnerships in Asia and the Middle East, and we are actively exploring opportunities to provide setmelanotide to patients in South America.

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 weight management in 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 early-onset, severe obesity and hyperphagia that are the result of genetic variants affecting the MC4R pathway, including BBS, Alström syndrome, certain variants of the POMC, PCSK1, LEPR, SRC1 and SH2B1 genes, as well as MC4R deficiency obesity. Bariatric surgery is not an appropriate 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. Also, existing therapies indicated for general obesity, including glucagon-like peptide-1 (GLP-1) receptor agonists, such as Wegovy®, and glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) agonists, such as tirzepatide which is being investigated as a treatment for obesity, do not specifically restore function impaired by genetic deficiencies in the MC4R pathway, which we believe is the root cause of hyperphagia and obesity in patients with MC4R genetic variants.

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 as of December 31, 2021, we have paid $4.0 million in clinical and regulatory milestones and $5.0 million in commercial 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. As of December 31, 2021, we have made $1.3 million of milestone payments to Camrus. 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.

RareStone Group Ltd.

In December 2021, we entered into an Exclusive License Agreement with RareStone, or the RareStone License. Pursuant to the RareStone License, we granted to RareStone an exclusive, sublicensable, royalty-bearing license under certain patent rights and know-how to develop, manufacture, commercialize and otherwise exploit any pharmaceutical product that contains setmelanotide in the diagnosis, treatment or prevention of conditions and diseases in humans in China, including mainland China, Hong Kong and Macao. RareStone has a right of first negotiation in the event that Rhythm chooses to grant a license to develop or commercialize the licensed product in Taiwan.

According to the terms of the RareStone License, RareStone has agreed to seek local approvals to commercialize IMCIVREE for the treatment of obesity and hyperphagia due to biallelic proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency, as well as Bardet-Biedl and Alström syndromes. Additionally, RareStone agreed to fund efforts to identify and enroll patients from China in Rhythm's global EMANATE trial, a Phase 3, randomized, double-blind, placebo-controlled trial to evaluate setmelanotide in five independent sub-studies in patients with obesity due to a heterozygous variant of POMC/PCSK1 or LEPR; certain variants of the SRC1 gene, certain variants of the SH2B1 gene, or PCSK1 N221D deletions within the MC4R pathway. According to the terms of the RareStone License, RareStone made an upfront payment to Rhythm of $7.0 million and issued $5.0 million in equity to Rhythm. Rhythm will be eligible to receive development and commercialization milestones of up to $62.5 million, as well as tiered royalty payments on annual net sales of IMCIVREE.

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, Braine 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. We have also entered into commercial supply agreements with both Polypeptide and Recipharm. Under our agreements, we pay these third parties for services and/or manufacture of setmelanotide 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 the future. In connection with our commercialization of setmelanotide or any future product candidate, we have engaged and could need to engage other third parties to assist in manufacturing and/or supply chain related aspects. While there are a limited number of companies that can produce raw materials and API in the quantities and with the quality and purity that we require for our product, based on our diligence to date, we believe our current network of manufacturing partners are able to fulfill these requirements, and are capable of continuing to expand capacity as needed. Additionally, we have, and will continue to evaluate further relationships with additional suppliers to increase overall capacity as well as further reduce risks associated with reliance on a limited number of suppliers for manufacturing. 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 additional capacity or seek alternate suppliers. We believe that our current suppliers and CMOs are able to scale production to meet our clinical and commercial demands. Because we rely on these CMOs, we have personnel with pharmaceutical development and manufacturing experience who are responsible for maintaining our CMO relationships.

Setmelanotide is distributed in the U.S. through our specialty pharmacy and in the EU/UK through third-party service providers that deliver the medication to patients. We plan to continue building out our network for commercial distribution in jurisdictions in which setmelanotide is approved.

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 NDA process or by comparable foreign regulatory authorities through similar applications before it may be legally marketed in the United States and in foreign jurisdictions. 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, progress reports summarizing the results of the clinical trials and nonclinical studies performed since the last progress report, among other information, 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.

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.

Foreign Regulation

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.

Regulation and Procedures Governing Marketing Authorization of Medicinal Products in the European Union

Non-clinical studies and clinical trials

Similarly to the United States, the various phases of non-clinical and clinical research in the EU are subject to significant regulatory controls.

Non-clinical studies are performed to demonstrate the health or environmental safety of new biological substances. Non-clinical studies must be conducted in compliance with the principles of good laboratory practice (GLP) as set forth in EU Directive 2004/10/EC. In particular, non-clinical studies, both *in vitro* and *in vivo*, must be planned, performed, monitored, recorded, reported and archived in accordance with the GLP principles, which define a set of rules and criteria for a quality system for the organizational process and the conditions for non-clinical studies. These GLP standards reflect the Organization for Economic Co-operation and Development requirements.

Clinical trials of medicinal products in the EU must be conducted in accordance with EU and national regulations and the International Conference on Harmonization (ICH) guidelines on good clinical practices (GCP) as well as the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki. If the sponsor of the clinical trial is not established within the EU, it must appoint an EU entity to act as its legal representative. The sponsor must take out a clinical trial insurance policy, and in most EU member states, the sponsor is liable to provide 'no fault' compensation to any study subject injured in the clinical trial.

The regulatory landscape related to clinical trials in the EU has been subject to recent changes. The EU Clinical Trials Regulation (CTR), which was adopted in April 2014 and repeals the EU Clinical Trials Directive, became applicable on January 31, 2022. Unlike directives, the CTR is directly applicable in all EU member states without the need for member states to further implement it into national law. The CTR notably harmonizes the assessment and supervision processes for clinical trials throughout the EU via a Clinical Trials Information System, which contains a centralized EU portal and database.

While the Clinical Trials Directive required a separate clinical trial application (CTA) to be submitted in each member state, to both the competent national health authority and an independent ethics committee, much like the FDA and IRB respectively, the CTR introduces a centralized process and only requires the submission of a single application to all member states concerned. The CTR allows sponsors to make a single submission to both the competent authority and an ethics committee in each member state, leading to a single decision per member state. The CTA must include, among other things, a copy of the trial protocol and an investigational medicinal product dossier containing information about the manufacture and quality of the medicinal product under investigation. The assessment procedure of the CTA has been harmonized as well, including a joint assessment by all member states concerned, and a separate assessment by each member state with respect to specific requirements related to its own territory, including ethics rules. Each member state's decision is communicated to the sponsor via the centralized EU portal. Once the CTA is approved, clinical study development may proceed.

The CTR foresees a three-year transition period. The extent to which ongoing and new clinical trials will be governed by the CTR varies. For clinical trials whose CTA was made under the Clinical Trials Directive before January 31, 2022, the Clinical Trials Directive will continue to apply on a transitional basis for three years. Additionally, sponsors may still choose to submit a CTA under either the Clinical Trials Directive or the CTR until January 31, 2023 and, if authorized, those will be governed by the Clinical Trials Directive until January 31, 2025. By that date, all ongoing trials will become subject to the provisions of the CTR.

Marketing Authorizations

In the EU, medicinal product candidates can only be commercialized after obtaining a marketing authorization, or MA. To obtain regulatory approval of a product candidate in the EU, we must submit a marketing authorization application, or MAA. The process for doing this depends, among other things, on the nature of the medicinal product.

There are two types of MAs:

- "Centralized MAs" are issued by the European Commission through the centralized procedure, based on the opinion of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) and are valid throughout the EU. The centralized procedure is mandatory for certain types of products, such as (i) medicinal products derived from biotechnological processes, (ii) designated orphan medicinal products, (iii) advanced therapy medicinal products (ATMPs) such as gene therapy, somatic cell-therapy or tissue-engineered medicines, and (iv) medicinal products containing a new active substance indicated for the treatment certain diseases, such as HIV/AIDS, cancer, neurodegenerative diseases, diabetes, auto-immune and other immune dysfunctions and viral diseases. The centralized procedure is optional for any products containing a new active substance not yet authorized in the EU, or for products that constitute a significant therapeutic, scientific or technical innovation or for which the granting of a MA would be in the interest of public health in the EU.

- "National MAs" are issued by the competent authorities of the EU member states, only cover their respective territory, and are available for product candidates not falling within the mandatory scope of the centralized procedure. Where a product has already been authorized for marketing in an EU member state, this national MA can be recognized in another member state through the mutual recognition procedure. If the product has not received a national MA in any member state at the time of application, it can be approved simultaneously in various member states through the decentralized procedure. Under the decentralized procedure an identical dossier is submitted to the competent authorities of each of the member states in which the MA is sought, one of which is selected by the applicant as the reference member state.

A MA has an initial validity for five years in principle. The MA 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 MA 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 MA was granted, at least six months before the MA 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 MA. Once subsequently definitively renewed, the MA shall be valid for an unlimited period. Any authorization which is not followed by the actual placing of the medicinal product on the EU market or on the market of the authorizing EU member state(s) within three years after authorization ceases to be valid (the so-called "sunset clause").

Under the centralized procedure, 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. In exceptional cases, the CHMP might perform an accelerated review of a MAA in no more than 150 days (not including clock stops). Innovative products that target an unmet medical need and are expected to be of major public health interest may be eligible for a number of expedited development and review programs, such as the PRIME scheme, which provides incentives similar to the breakthrough therapy designation in the U.S. In March 2016, the EMA launched an initiative, the Priority Medicines (PRIME) scheme, a voluntary scheme aimed at enhancing the EMA's support for the development of medicines that target unmet medical needs. It is based on increased interaction and early dialogue with companies developing promising medicines, to optimize their product development plans and speed up their evaluation to help them reach patients earlier. Product developers that benefit from PRIME designation can expect to be eligible for accelerated assessment but this is not guaranteed. Many benefits accrue to sponsors of product candidates with PRIME designation, including but not limited to, early and proactive regulatory dialogue with the EMA, frequent discussions on clinical trial designs and other development program elements, and accelerated MAA assessment once a dossier has been submitted. Importantly, a dedicated contact and rapporteur from the CHMP is appointed early in the PRIME scheme facilitating increased understanding of the product at EMA's committee level. An initial meeting initiates these relationships and includes a team of multidisciplinary experts at the EMA to provide guidance on the overall development and regulatory strategies.

Moreover, in the EU, a "conditional" MA may be granted in cases where all the required safety and efficacy data are not yet available. The conditional MA is subject to conditions to be fulfilled for generating the missing data or ensuring increased safety measures. It is valid for one year and has to be renewed annually until fulfillment of all the conditions. Once the pending studies are provided, it can become a "normal" MA. However, if the conditions are not fulfilled within the timeframe set by the EMA, the MA ceases to be renewed. Furthermore, MA may also be granted "under exceptional circumstances" when the applicant can show that it is unable to provide comprehensive data on the efficacy and safety under normal conditions of use even after the product has been authorized and subject to specific procedures being introduced. This may arise in particular when the intended indications are very rare and, in the present state of scientific knowledge, it is not possible to provide comprehensive information, or when generating data may be contrary to generally accepted ethical principles. This MA is close to the conditional MA as it is reserved for medicinal products to be approved for severe diseases or unmet medical needs and the applicant does not hold the complete data set legally required for the grant of a MA. However, unlike the conditional MA, the applicant does not have to provide the missing data and will never have to. Although the MA "under exceptional circumstances" is granted definitively, the risk-benefit balance of the medicinal product is reviewed annually and the MA is withdrawn in case the risk-benefit ratio is no longer favorable.

Data and marketing exclusivity

The EU also provides opportunities for market exclusivity. Upon receiving MA, reference product candidates generally receive eight years of data exclusivity and an additional two years of market exclusivity. If granted, the data exclusivity period prevents applicants generic or biosimilar applicants from relying on the pre-clinical and clinical trial data contained in the dossier of the reference product when applying for a generic or biosimilar MA in the EU during a period of eight years from the date on which the reference product was first authorized in the EU. During the market exclusivity period, an application for a generic or biosimilar MA can be submitted and a related MA may be granted, and the innovator's data may be referenced, but no generic or biosimilar can be placed on the EU market until 10 years have elapsed from the initial MA of the reference product in the EU. The overall ten-year period can be extended to a maximum of eleven years if, during the first eight years of those ten years, the MA 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. However, there is no guarantee that a product will be considered by the EU's regulatory authorities to be a new chemical entity, and products may not qualify for data exclusivity.

Orphan Medicinal Products

The criteria for designating an "orphan medicinal product" in the EU are similar in principle to those in the United States. Regulation (EC) No. 141/2000, as implemented by Regulation (EC) No. 847/2000 provides that a medicinal product can be designated as an orphan if its sponsor can establish that: (1) the product is intended for the diagnosis, prevention or treatment of a life threatening or chronically debilitating condition; (2) either (a) such condition affects not more than five in ten thousand persons in the EU when the application is made, or (b) the product, without the benefits derived from the orphan status, would not generate sufficient return in the EU to justify the necessary investment; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the EU or, if such method exists, the medicinal product will be of significant benefit to those affected by that condition.

In the EU, an application for designation as an orphan product can be made any time prior to the filing of the application for MA. Orphan drug designation entitles a party to incentives such fee reductions or fee waivers, protocol assistance, and access to the centralized procedure. Once authorized, orphan medicinal products are entitled to a ten-years period of market exclusivity for the approved therapeutic indication, which means that the competent authorities cannot accept another MAA, or grant a MA, or accept an application to extend a MA for a similar product for the same indication for a period of ten years. The period of market exclusivity is extended by two years for orphan medicinal products that have also complied with an agreed pediatric investigation plan (PIP). No extension to any supplementary protection certificate can be granted on the basis of pediatric studies for orphan indications. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

The orphan exclusivity period may, however, be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for which it received orphan drug destination, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity, or where the prevalence of the condition has increased above the threshold. Granting of an authorization for another similar orphan medicinal product where another product has market exclusivity can happen at any time if: (i) the second applicant can establish that its product, although similar to the authorized product, is safer, more effective or otherwise clinically superior, (ii) inability of the applicant to supply sufficient quantities of the orphan medicinal product or (iii) where the applicant consents to a second orphan medicinal product application. A company may voluntarily remove a product from the orphan register.

Pediatric Development

In the EU, MAAs for new medicinal products have to include the results of trials conducted in the pediatric population, in compliance with a PIP agreed with the EMA's Pediatric Committee (PDCO). The PIP sets out the timing and measures proposed to generate data to support a pediatric indication of the drug for which an MA is being sought. The PDCO can grant a deferral of the obligation to implement some or all of the measures of the PIP until there are sufficient data to demonstrate the efficacy and safety of the product in adults. Further, the obligation to provide pediatric clinical trial data can be waived by the PDCO when these data are not needed or appropriate because the product is likely to be

ineffective or unsafe in children, the disease or condition for which the product is intended occurs only in adult populations, or when the product does not represent a significant therapeutic benefit over existing treatments for pediatric patients. Once the MA is obtained in all member states and study results are included in the product information, even when negative, the product is eligible for a six-months supplementary protection certificate extension (if any is in effect at the time of approval) or, in the case of orphan pharmaceutical products, a two year extension of the orphan market exclusivity is granted.

Post-Approval Requirements

Similar to the United States, both MA holders and manufacturers of medicinal products are subject to comprehensive regulatory oversight by the EMA, the European Commission and/or the competent regulatory authorities of the member states. The holder of a MA must establish and maintain a pharmacovigilance system and appoint an individual qualified person for pharmacovigilance who is responsible for oversight of that system. Key obligations include expedited reporting of suspected serious adverse reactions and submission of periodic safety update reports (PSURs).

All new MAA must include a risk management plan (RMP) describing the risk management system that the company will put in place and documenting measures to prevent or minimize the risks associated with the product. The regulatory authorities may also impose specific obligations as a condition of the MA. Such risk-minimization measures or post-authorization obligations may include additional safety monitoring, more frequent submission of PSURs, or the conduct of additional clinical trials or post-authorization safety studies.

The advertising and promotion of medicinal products is also subject to laws concerning promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices. All advertising and promotional activities for the product must be consistent with the approved summary of product characteristics, and therefore all off-label promotion is prohibited. Direct-to-consumer advertising of prescription medicines is also prohibited in the EU. Although general requirements for advertising and promotion of medicinal products are established under EU directives, the details are governed by regulations in each member state and can differ from one country to another.

The aforementioned EU rules are generally applicable in the European Economic Area (EEA) which consists of the 27 EU member states plus Norway, Liechtenstein and Iceland.

Failure to comply with EU and member state laws that apply to the conduct of clinical trials, manufacturing approval, MA of medicinal products and marketing of such products, both before and after grant of the MA, manufacturing of pharmaceutical products, statutory health insurance, bribery and anti-corruption or with other applicable regulatory requirements may result in administrative, civil or criminal penalties. These penalties could include delays or refusal to authorize the conduct of clinical trials, or to grant MA, product withdrawals and recalls, product seizures, suspension, withdrawal or variation of the MA, total or partial suspension of production, distribution, manufacturing or clinical trials, operating restrictions, injunctions, suspension of licenses, fines and criminal penalties.

Brexit and the Regulatory Framework in the United Kingdom

The United Kingdom (UK) left the EU on January 31, 2020, following which existing EU medicinal product legislation continued to apply in the UK during the transition period under the terms of the EU-UK Withdrawal Agreement. The transition period, which ended on December 31, 2020, maintained access to the EU single market and to the global trade deals negotiated by the EU on behalf of its members. The transition period provided time for the UK and EU to negotiate a framework for partnership for the future, which was then crystallized in the Trade and Cooperation Agreement (TCA) and became effective on the January 1, 2021. The TCA includes specific provisions concerning pharmaceuticals, which include the mutual recognition of GMP inspections of manufacturing facilities for medicinal products and GMP documents issued, but does not foresee wholesale mutual recognition of UK and EU pharmaceutical regulations.

EU laws which have been transposed into UK law through secondary legislation continue to be applicable as “retained EU law”. However, new legislation such as the EU CTR or in relation to orphan medicines will not be applicable. The UK government has passed a new Medicines and Medical Devices Act 2021, which introduces delegated powers in

favour of the Secretary of State or an 'appropriate authority' to amend or supplement existing regulations in the area of medicinal products and medical devices. This allows new rules to be introduced in the future by way of secondary legislation, which aims to allow flexibility in addressing regulatory gaps and future changes in the fields of human medicines, clinical trials and medical devices.

As of January 1, 2021, the Medicines and Healthcare products Regulatory Agency (MHRA) is the UK's standalone medicines and medical devices regulator. As a result of the Northern Ireland protocol, different rules will apply in Northern Ireland than in England, Wales, and Scotland, together, Great Britain (GB); broadly, Northern Ireland will continue to follow the EU regulatory regime, but its national competent authority will remain the MHRA. The MHRA has published a guidance on how various aspects of the UK regulatory regime for medicines will operate in GB and in Northern Ireland following the expiry of the Brexit transition period on December 31, 2020. The guidance includes clinical trials, importing, exporting, and pharmacovigilance and is relevant to any business involved in the research, development, or commercialization of medicines in the UK. The new guidance was given effect via the Human Medicines Regulations (Amendment etc.) (EU Exit) Regulations 2019 (the Exit Regulations).

The MHRA has introduced changes to national licensing procedures, including procedures to prioritize access to new medicines that will benefit patients, including a 150-day assessment and a rolling review procedure. All existing EU MAs for centrally authorized products were automatically converted or grandfathered into UK MAs, effective in GB (only), free of charge on January 1, 2021, unless the MA holder chooses to opt-out. After Brexit, companies established in the UK cannot use the centralized procedure and instead must follow one of the UK national authorization procedures or one of the remaining post-Brexit international cooperation procedures to obtain an MA to commercialize products in the UK. The MHRA may rely on a decision taken by the European Commission on the approval of a new (centralized procedure) MA when determining an application for a GB authorization; or use the MHRA's decentralized or mutual recognition procedures which enable MAs approved in EU member states (or Iceland, Liechtenstein, Norway) to be granted in GB.

Additionally, an MHRA public consultation on the post-Brexit regulatory framework for medical devices and diagnostics was opened until end of November 2021. MHRA seeks to amend the UK Medical Devices Regulations 2002 (which are based on EU legislation, primarily the EU Medical Devices Directive and the EU In Vitro Diagnostic Medical Devices Directive), in particular to create new access pathways to support innovation, create an innovative framework for regulating software and artificial intelligence as medical devices, reform *in vitro* diagnostic medical devices regulation, and foster sustainability through the reuse and remanufacture of medical devices. The new regime is expected to come into force in July 2023, coinciding with the end of the acceptance period for EU CE marks in Great Britain, subject to appropriate transitional arrangements.

Regulation of Combination Products in the European Union

The EU regulates medical devices and medicinal products separately, through different legislative instruments, and the applicable requirements will vary depending on the type of drug-device combination product. EU guidance has been published to help manufacturers select the right regulatory framework.

Drug-delivery products intended to administer a medicinal product where the medicinal product and the device form a single integral product are regulated as medicinal products in the EU. The EMA is responsible for evaluating the quality, safety and efficacy of MAAs submitted through the centralized procedure, including the safety and performance of the medical device in relation to its use with the medicinal product. The EMA or the EU member state national competent authority will assess the product in accordance with the rules for medicinal products described above but the device part must comply with the EU Medical Devices Regulation (including the general safety and performance requirements provided in Annex I). MAA must include – where available – the results of the assessment of the conformity of the device part with the Medical Devices Regulation contained in the manufacturer's EU declaration of conformity of the device or the relevant certificate issued by a notified body. If the MAA does not include the results of the conformity assessment and where for the conformity assessment of the device, if used separately, the involvement of a notified body is required, the competent authority must require the applicant to provide a notified body opinion on the conformity of the device.

By contrast, in case of drug-delivery products intended to administer a medicinal product where the device and the medicinal product do not form a single integral product (but are e.g. co-packaged), the medicinal product is regulated in accordance with the rules for medicinal products described above while the device part is regulated as a medical device and will have to comply with all the requirements set forth by the Medical Devices Regulation. The characteristics of non-integral devices used for the administration of medicinal products may impact the quality, safety and efficacy profile of the medicinal products. To the extent that administration devices are co-packaged with the medicinal product or, in exceptional cases, where the use of a specific type of administration device is specifically provided for in the product information of the medicinal product, additional information may need to be provided in the MAA for the medicinal product on the characteristics of the medical device(s) that may impact on the quality, safety and/or efficacy of the medicinal product.

The requirements regarding quality documentation for medicinal products when used with a medical device, including single integral products, co-packaged and referenced products, are outlined in the EMA guideline of July 22, 2021, which became effective on January 1, 2022.

The aforementioned EU rules are generally applicable in the EEA.

Regulation of Companion Diagnostics in the European Union

In the EU, *in vitro* diagnostic medical devices are regulated by Directive 98/79/EC (IVDD) which regulates the placing on the market, the CE marking, the essential requirements, the conformity assessment procedures, the registration obligations for manufactures and devices as well as the vigilance procedure. *In vitro* diagnostic medical devices must comply with the requirements provided for in the Directive, and with further requirements implemented at national level (as the case may be).

The regulation of companion diagnostics will be subject to further requirements once the in-vitro diagnostic medical devices Regulation No 2017/746 (IVDR) will become applicable on May 26, 2022. However on October 14, 2021, the European Commission proposed a “progressive” roll-out of the IVDR to prevent disruption in the supply of *in vitro* diagnostic medical devices. The European Parliament and Council adopted the proposed regulation on December 15, 2021. The IVDR will fully apply on May 26, 2022 but there will be a tiered system extending the grace period for many devices (depending on their risk classification) before they have to be fully compliant with the regulation.

The IVDR introduces a new classification system for companion diagnostics which are now specifically defined as diagnostic tests that support the safe and effective use of a specific medicinal product, by identifying patients that are suitable or unsuitable for treatment. Companion diagnostics will have to undergo a conformity assessment by a notified body. Before it can issue a CE certificate, the notified body must seek a scientific opinion from the EMA on the suitability of the companion diagnostic to the medicinal product concerned if the medicinal product falls exclusively within the scope of the centralized procedure for the authorization of medicines, or the medicinal product is already authorized through the centralized procedure, or a MAA for the medicinal product has been submitted through the centralized procedure. For other substances, the notified body can seek the opinion from a national competent authorities or the EMA.

The aforementioned EU rules are generally applicable in the EEA.

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 EU, pricing and reimbursement schemes vary widely from one member state to another. Some member states 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 (HTA), in order to obtain reimbursement or pricing approval. For example, the EU 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.

HTA of medicinal products is, however, becoming an increasingly common part of the pricing and reimbursement procedures in some EU member states, including 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.

On January 15, 2021, Regulation No 2021/2282 on HTA, amending Directive 2011/24/EU, was adopted. This regulation intends 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 regulation foresees a three-year transitional period and will 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.

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 non-physician practitioners (physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists, anesthesiology assistants, and certified nurse midwives) 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 national laws (including anti-bribery laws) of the EU member states. In the UK, the UK Bribery Act 2010 applies to any company incorporated in or "carrying on business", 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/or 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 legislation and national laws on medicinal products including on the promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices, 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 significant penalties.

For example, HIPAA, as amended by the Health Information Technology for Economic and Clinical Health, and the regulations implemented thereunder, or collectively, HIPAA, imposes 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. The California Privacy Rights Act, or CPRA, was also 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 will 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 at both the federal and state level, as well in the EU and other jurisdictions that could impose new obligations or limitations in areas affecting our business. 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, fines, and demands or orders that we modify or cease existing business practices.

The EU, UK, Switzerland and other countries have also adopted data protection laws and regulations, which impose significant compliance obligations. In the EEA, the collection and use of personal data (including health data) is governed by the provisions of the General Data Protection Regulation (GDPR). From January 1, 2021, we are also subject to the UK data protection regime, consisting primarily of the UK General Data Protection Regulation and the UK Data Protection Act 2018 (together, the "UK GDPR"), which retains in large part the GDPR in UK national law following Brexit. The GDPR, together with the UK GDPR, imposes a strict data protection compliance regime in relation to our collection, control, processing, sharing, disclosure and other use of data relating to identifiable living individuals ("personal data") within the EEA and/or UK. Fines for certain breaches of the GDPR and the UK GDPR are significant, up to the greater of (i) 20 million Euros (for the GDPR) and 17.5 million pounds (for the UK GDPR), or (ii) 4 % of total global annual turnover. In addition to the foregoing, a breach of the GDPR or UK GDPR could result in regulatory investigations, reputational damage, orders to cease/change our processing of 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.

The GDPR, together with the national legislation of the EEA member states governing the processing of personal data, and the UK GDPR 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 EEA and the UK, 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 EEA member states may interpret the GDPR and national laws differently and impose additional requirements, including in relation to health data, which add to the complexity of processing personal data in the EEA. Guidance on implementation and compliance practices are often updated or otherwise revised.

With respect to the transfers of personal data out of the EEA and the UK, the GDPR and the UK GDPR provide that the transfers of personal data to countries that are not considered to provide an adequate level of data protection, including the United States, are 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. While the CJEU upheld the adequacy of an alternative mechanism, the standard contractual clauses (a standard form of contract approved by the European Commission as an adequate personal data transfer mechanism), it made clear that reliance on them alone may not necessarily be sufficient to enable data transfers in all circumstances. Use of the standard contractual clauses must now be assessed on a case-by-case basis taking into account the legal regime applicable in the destination country, in particular applicable surveillance laws and rights of individuals and additional measures and/or contractual provisions may need to be put in place, however, the nature of these additional measures is currently uncertain. Additionally, the European Commission has published revised standard contractual clauses for data transfers from the EEA: the revised clauses must be used for relevant new data transfers from September 27, 2021; existing standard contractual clauses arrangements must be migrated to the revised clauses by December 27, 2022. The revised standard contractual clauses apply only to the transfer of personal data outside of the EEA and not the UK; the UK's Information Commissioner's Office launched a public consultation on its draft revised data transfers mechanisms in August 2021. 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.

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. On June 17, 2021, the U.S. Supreme Court dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the ACA. Thus, the ACA will remain in effect in its current form. Further, prior to the U.S. Supreme Court ruling, President Biden issued an executive order to initiate a special enrollment period from February 15, 2021, through August 15, 2021, for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA.

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 % 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, 2022, 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, 2022, we had approximately 140 employees, about 80 of which are located near our corporate headquarters in Boston. We spent much of 2021 building out our U.S. field presence and enhancing our global footprint and now have approximately 40 employees located in various parts of the United States and nearly 20 employees across Europe. 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, hire and retain highly skilled employees. We emphasize several 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 frequently assess the external market to 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 open

communication, measure employee engagement and identify opportunities for improvement. Throughout the COVID-19 pandemic, we have implemented efforts to ensure our employees are enabled to take advantage of flexible working arrangements and collaborate safely.

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 global 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 inspired to 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 significant 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. To date, we have not generated significant revenue from product sales. We have obtained FDA approval for IMCIVREE 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. IMCIVREE has also received marketing authorization from the European Commission and Great Britain's Medicines and Healthcare Products Regulatory Agency, or MHRA for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. We have not obtained any other regulatory approvals for setmelanotide. We first commercialized IMCIVREE in the U.S. in the first quarter of 2021 and 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 approved by the FDA and authorized by the European Commission and the MHRA, as noted above, and is in development to address patients with Bardet-Biedl syndrome, or BBS, Alström syndrome, and several 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 $69.6 million and $134.0 million for the years ended December 31, 2021 and 2020, respectively. As of December 31, 2021, we had an accumulated deficit of $528.9 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 significant revenue from setmelanotide. 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;
- 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 confirmed by genetic testing and authorized in the EU and Great Britain for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above, 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 the EU and Great Britain 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, 2021, our cash and cash equivalents and short-term investments were approximately $294.9 million. We expect our cash and cash equivalents and short-term investments will enable us to fund our operating expenses into 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

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 impairments 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 diseases of extreme and unrelenting appetite and obesity. We hypothesize that patients with other upstream genetic variants in the MC4R pathway may also respond with reductions in weight and hunger after treatment with setmelanotide. However, patients with other upstream genetic variants may not have a similar response to setmelanotide, and until we obtain more clinical data in other genetic variants, we will not be sure that we can achieve proof of concept in such indications.

We are actively working to advance additional genetic variants related to the MC4R pathway through our clinical development program. Our continued development efforts are focused on obesity related to several single gene related, or monogenic, MC4R pathway impairments: Bardet Biedl syndrome, or BBS; Alström syndrome; 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 steroid receptor coactivator 1, or SRC1, variants; obesity due to SH2B adapter protein 1, or SH2B1; hypothalamic obesity; and MC4R deficiency obesity. For example, in the first half of 2022 we plan to initiate our pivotal Phase 3 EMANATE clinical trial of setmelanotide. The trial is a randomized, double-blind, placebo-controlled study with five independent sub-studies evaluating setmelanotide in patients with: heterozygous POMC/PCSK1 obesity; heterozygous LEPR obesity; certain variants of the SRC1; certain variants of SH2B1 genes; or PCSK1 N221D deletions within the MC4R pathway. Each sub-study will be entirely independent of the others and, if successful, is designed to support separate regulatory submissions to the FDA and EMA in each studied indication. However, the FDA and EMA may not view positive results in one sub-study, even if such results are statistically significant and clinically meaningful, as being sufficient for approval for any given indication.

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 such 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 or foreign regulatory authorities. If we fail to obtain positive results in our Phase 3 clinical trials of setmelanotide, the development timeline and regulatory approval and commercialization prospects for setmelanotide and, correspondingly, our business and financial prospects, would be materially adversely affected.

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. 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, in January 2021 we announced interim data from our ongoing exploratory Phase 2 Basket Study evaluating setmelanotide in patients with MC4R pathway genetic variants 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 variants 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 45,000 patients, as of December 31, 2021, with severe obesity that provide another approach to estimating prevalence. Since the published epidemiology studies for these genetic variants

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 adults with severe obesity (body mass index, or BMI, greater than 40 kg/m^2) and for children with severe early-onset obesity (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 diseases), 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 adults with severe obesity (BMI, greater than 40 kg/m^2) and for children with severe early-onset obesity (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 diseases 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 in the United States. This estimate is based on:
    - published prevalence estimates of one in 1,000,000 in North America, which projects to approximately 325 people in the United States. We believe the majority of these patients are addressable patients; and
    - our belief that with wider availability of genetic testing expected for Alström syndrome and increased awareness of new treatments, the number of patients diagnosed with this disorder will increase.
- *POMC, PCSK1, or LEPR Heterozygous Obesities; SRC1 and SH2B1 Obesities*. Our potential setmelanotide-responsive patient population estimate for POMC, PCSK1, or LEPR heterozygous, SRC1 and SH2B1 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.
- *Hypothalamic obesity*. Our addressable patient population estimate for hypothalamic obesity (HO) is greater than 4,500 patients in the United States. This estimate is based on:

- an annual incidence of craniophryngioma (CP) of approximately 1.3 million per year in the United States, which projects to approximately 493 cases of CP per year based on a United States population of approximately 329 million;
- approximately 62.5% (based on a published range of 50% to 75%) of CP patients develop HO;
- 20-year average survival after CP surgery of 75% (based on a published range of 66% to 85%);
- allowing for patients that develop HO due to other factors besides CP, results in an estimated HO prevalence in the United States exceeding 4,500 patients; and
- internal Company estimate is based on reported incidence of hypothalamic obesity following craniophryngioma and long-term survival rates.

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 diseases 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, including general obesity, 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 participants, 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, at a minimum 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, or similar foreign application 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 and regions, 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;
- further 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;
- interruptions or delays in manufacturing activities due to restricted or limited operations at our CMOs;
- delays in global shipping of raw materials, API, and/or finished goods between locations;
- interruptions or delays in delivery of clinical trial ancillary supplies, due to restricted or limited operations;
- 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;
- continued limitations in employee resources that would otherwise be focused on the start-up or 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, or due to increased hiring and/or retention or other staffing issues;
- refusal of the FDA or foreign regulatory authorities 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 duration and severity of the pandemic, the impact of the variants, travel restrictions and social distancing recommendations and regulations in the United States and other countries, business closures or business disruptions, the effectiveness of vaccines, vaccine distribution efforts and treatments, 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 skin darkening. These effects have generally been reversible in clinical trials after discontinuation of setmelanotide, 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 EU competent authorities 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.

We may not be able to obtain or maintain orphan drug designations for setmelanotide or to obtain or maintain 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 of the EMA's Committee for Orphan Medicinal Products. A medicinal product may be designated as orphan if its sponsor can establish that (i) the product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition; (ii) either (a) such condition affects no more than 5 in 10,000 persons in the EU when the application is made, or (b) the product, without the benefits derived from orphan status, would not generate sufficient return in the EU to justify investment; and (iii) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the EU, or if such a method exists, the medicinal product will be of significant benefit to those affected by the condition. The application for orphan designation must be submitted before the application for marketing authorization.

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, protocol assistance, and access to the centralized marketing authorization procedure. Orphan drug designation must be requested before submitting an application for marketing authorization. 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 for the approved therapeutic indication, which means that the EMA and European Commission cannot accept another marketing authorization application, grant a marketing authorization, or accept an application to extend a marketing authorization for a similar product for the same indication for a period of ten years. The period of market exclusivity is extended by two years for orphan medicinal products that have also complied with an agreed Pediatric Investigation Plan, or PIP. No extension to any supplementary protection certificate can be granted on the basis of pediatric studies for orphan indications. Orphan medicinal product designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. 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.

The ten-year market exclusivity in the EU may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for which it received orphan designation, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity, or where the prevalence of the condition has increased above the threshold. Additionally granting of an authorization for another similar orphan medicinal product where another product has market exclusivity can happen at any time: (i) the second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior; (ii) the applicant cannot supply enough orphan medicinal product or (iii) where the applicant consents to a second orphan medicinal product application. Orphan drug designation does not, in itself, convey any advantage in, or shorten the duration of, the regulatory review and authorization process.

In connection with IMCIVREE's approval, the FDA granted us seven years of orphan drug exclusivity for setmelanotide 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, and in the EU, we obtained ten years of market exclusivity for setmelanotide for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above.

We have also been granted orphan drug designation for setmelanotide for the treatment of BBS and Alström syndrome in both the United States and the EU. Setmelanotide has also been granted orphan designation for setmelanotide in treating Prader-Willi syndrome in the EU. There can be no assurance that we will be able to maintain the benefits orphan drug exclusivity, or that the FDA or the European Commission will grant orphan designations 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 though we have obtained orphan drug exclusivity for certain uses of setmelanotide, such exclusivities 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 for setmelanotide for the treatment of obesity and the control of hunger associated with deficiency disorders of the MC4R receptor pathway and Breakthrough Therapy designation for setmelanotide for the treatment of obesity associated with certain 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 or PRIME designation by the EMA 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 additional marketing authorizations in the EU.

The FDA is authorized under the FDCA to give certain product candidates "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, 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 scheme was launched by the EMA in 2016. In the EU, innovative products that target an unmet medical need and are expected to be of major public health interest may be eligible for a number of expedited development and review programs, such as the PRIME scheme, which provides incentives similar to the Breakthrough Therapy designation in the United States. PRIME is a voluntary scheme aimed at enhancing the EMA's support for the development of medicines that target unmet medical needs. It is based on increased interaction and early dialogue with companies developing promising medicines, to optimize their product development plans and speed up their evaluation to help them reach patients earlier. The benefits of a PRIME designation include the appointment of a rapporteur before submission of a 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. In late June 2018, setmelanotide was granted eligibility to PRIME by the CHMP for the treatment of obesity and the control of hunger associated with deficiency disorders of the MC4R receptor pathway. 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 additional marketing authorizations 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 and syringes. 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. 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.

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 six years of age and older with obesity due to POMC, PCSK1 or LEPR deficiencies, as confirmed by genetic testing, 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 certification 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 certification 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.

In the EU, in vitro diagnostic medical devices are regulated by Directive 98/79/EC, or the IVDD. The regulation of companion diagnostics will be subject to further requirements once the in-vitro diagnostic medical devices Regulation No 2017/746, or the IVDR, will become applicable on May 26, 2022. However on October 14, 2021, the European Commission proposed a "progressive" roll-out of the IVDR to prevent disruption in the supply of in vitro diagnostic

medical devices. The European Parliament and Council adopted the proposed regulation on December 15, 2021. The IVDR will fully apply on May 26, 2022 but there will be a tiered system extending the grace period for many devices (depending on their risk classification) before they have to be fully compliant with the regulation. The IVDR introduces a new classification system for companion diagnostics which are now specifically defined as diagnostic tests that support the safe and effective use of a specific medicinal product, by identifying patients that are suitable or unsuitable for treatment. Companion diagnostics will have to undergo a conformity assessment by a notified body. Before it can issue a CE certificate, the notified body must seek a scientific opinion from the EMA on the suitability of the companion diagnostic to the medicinal product concerned if the medicinal product falls exclusively within the scope of the centralized procedure for the authorization of medicines, or the medicinal product is already authorized through the centralized procedure, or a marketing authorization application for the medicinal product has been submitted through the centralized procedure. For other substances, the notified body can seek the opinion from a national competent authorities or the EMA. Compliance with the new requirements may impact our development plans for setmelanotide.

If the FDA or a comparable regulatory authority requires clearance, approval or certification 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 certification of, 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. In January 2022, the FDA granted the *de novo* request for classification for the POMC/PCSK1/LEPR CDx Panel for market authorization as a Class II device. If the FDA or a comparable regulatory authority requires clearance, approval or certification 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 certification of, 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 operationalize, 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 start-up, 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, among others, 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 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 and foreign regulatory authorities enforce these regulations and GCP 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 GCPs, 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 or foreign regulatory authorities will determine that any of our clinical trials comply with GCPs. In addition, our clinical trials must be conducted with products produced under current Good Manufacturing Practices, or cGMPs and similar foreign requirements. 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 for which we obtain approval 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 IMCIVREE 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 successfully commercialize IMCIVREE or any other product candidates for which we obtain approval 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, such as IMCIVREE, and, as a result, they may not cover or provide adequate payment. Even if we show improved efficacy or improved convenience of administration, 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 IMCIVREE 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 IMCIVREE 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, Great Britain 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 IMCIVREE with other available therapies. If reimbursement for IMCIVREE 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 IMCIVREE 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 the United Kingdom 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.

On January 15, 2021, Regulation No 2021/2282 on HTA, amending Directive 2011/24/EU, was adopted. This regulation intends 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 regulation foresees a three-year transitional period and will 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.

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, and the European Commission and MHRA granted marketing authorization to IMCIVREE, for the treatment of obesity and the control of hunger associated with confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above, 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, the European Union and Great Britain.

We intend to seek marketing authorizations in various countries worldwide. In order to market any product outside of the United States, the EU or Great Britain, 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 or marketing authorization from the European Commission or the MHRA. 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 and Europe, 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 IMCIVREE.

The commercial success of IMCIVREE will also depend upon the awareness and acceptance of IMCIVREE 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 patients with obesity;
- 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 or other specific obligations as a condition of approval or post-approval, may not agree with our proposed REMS or other specific obligations, or may impose additional requirements that limit the promotion, advertising, distribution or sales of IMCIVREE.

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, and hypothalamic obesity. Bariatric surgery is not a good 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. Also, existing therapies indicated for general obesity, including glucagon-like peptide-1 (GLP-1) receptor agonists, such as Wegovy®, and glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) agonists, such as tirzepatide which is being investigated as a treatment for obesity, do not specifically restore function impaired by genetic deficiencies in the MC4R pathway, which we believe is the root cause of hyperphagia and obesity in patients with MC4R genetic variants. 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 and commercial product 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. 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 GMP and similar foreign 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 Switzerland, LLC, or Corden, (formerly Peptisyntha SA prior to its acquisition by Corden), and Neuland Laboratories for certain process development and manufacturing services for regulatory starting materials and/or raw materials in connection with the manufacture of setmelanotide. We have entered into long-term commercial supply agreements with PolyPeptide Group and Recipharm Monts S.A.S. for manufacturing of drug substance and drug product for IMCIVREE. 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 GMPs and similar foreign requirements for manufacture of both drug substance, or 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 GMPs and similar foreign requirements, 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 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 have been affected, which has disrupted 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 all of our contractors involved with the manufacturing of our weekly formulation of setmelanotide. We currently place individual batch or campaign orders with the CMOs/suppliers that are individually contracted under existing master services and quality agreements for the weekly formulation of setmelanotide. 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 and foreign regulatory authorities 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.

The exclusive license agreement with RareStone Group Ltd., or RareStone, is important to our business. If we or RareStone fail to adequately perform under the agreement, or if we or RareStone terminate the agreement, the development of setmelanotide in certain indications and commercialization of IMCIVREE in certain markets would be delayed or terminated and our business would be adversely affected.

In December 2021, we entered into an Exclusive License Agreement with RareStone, or the RareStone License. Pursuant to the RareStone License, we granted to RareStone an exclusive, sublicensable, royalty-bearing license under certain patent rights and know-how to develop, manufacture, commercialize and otherwise exploit any pharmaceutical product that contains setmelanotide in the diagnosis, treatment or prevention of conditions and diseases in humans in China, including mainland China, Hong Kong and Macao. RareStone has a right of first negotiation in the event that the Company chooses to grant a license to develop or commercialize the licensed product in Taiwan.

Termination of this RareStone License could cause significant delays in our product development and commercialization efforts for setmelanotide and could prevent us from commercializing IMCIVREE in the markets covered by the RareStone License without first expanding our internal capabilities or entering into another agreement with a third party. Any alternative collaboration or license could also be on less favorable terms to us. In addition, under the agreement, RareStone agreed to provide funding for certain clinical development activities. If the agreement were terminated, we may need to refund those payments and seek additional financing to support the research and development of any terminated products or discontinue any terminated products, which could have a material adverse effect on our business.

Under the RareStone License, we are dependent upon RareStone to successfully commercialize any applicable collaboration products in China, including mainland China, Hong Kong and Macao. We cannot directly control RareStone's commercialization activities or the resources it allocates to setmelanotide. Our interests and RareStone's interests may differ or conflict from time to time, or we may disagree with RareStone's level of effort or resource allocation. RareStone may internally prioritize setmelanotide differently than we do or it may not allocate sufficient resources to effectively or optimally commercialize setmelanotide. If these events were to occur, our business would be adversely affected.

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.

While we have registered trademarks for the commercial trade name IMCIVREE (setmelanotide) in the United States and the EU, we have not yet obtained trademark protection for IMCIVREE in certain foreign jurisdictions and failure to secure such registrations could adversely affect our business.

While we have received registered trademarks for the commercial trade name IMCIVREE (setmelanotide) and its logo in the United States and the EU, we have not yet 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.

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 and the marketing authorizations granted by the European Commission and the MHRA for the treatment of obesity and the control of hunger associated with confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above in the EU and Great Britain, respectively. We depend primarily 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 (IMCIVREE), which is currently approved by FDA for chronic weight management in patients with obesity due to POMC, PCSK1 or LEPR deficiencies and by the European Commission and MHRA for the treatment of obesity and the control of hunger associated with confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above, 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 EU and Great Britain. 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 nonclinical 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 postmarketing 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 or 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 for additional indications 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 based on the EMA's opinion 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 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.

Future regulatory legislation or regulation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates.

The EU pharmaceutical legislation is currently undergoing a complete review process, in the context of the Pharmaceutical Strategy for Europe initiative, launched by the European Commission in November 2020. A proposal for revision of several legislative instruments related to medicinal products (potentially revising the duration of regulatory exclusivity, eligibility for expedited pathways, etc.) is expected to be adopted by the European Commission by the end of 2022. The proposed revisions, once they are agreed and adopted by the European Parliament and European Council (not expected before the end of 2024), may have a significant impact on the pharmaceutical industry in the long term.

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 and foreign regulatory authorities 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 and foreign regulatory authorities' ability to hire and retain key personnel and accept the payment of user fees, and other events that may otherwise affect the FDA's and foreign regulatory authorities' ability to perform routine functions. Average review times at the FDA and foreign regulatory authorities 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, such as the EMA, following its relocation to Amsterdam and resulting staff changes, 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, , 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 the COVID-19 pandemic, in March 2020, the FDA announced its intention to postpone most inspections of foreign manufacturing facilities, and on March 18, 2020, the FDA temporarily postponed routine surveillance inspections of domestic manufacturing facilities. Subsequently, in July 2020, the FDA resumed certain on-site inspections of domestic manufacturing facilities subject to a risk-based prioritization system. The FDA utilized this risk-based assessment system to assist in determining when and where it was safest to conduct prioritized domestic inspections. Additionally, on April 15, 2021, the FDA issued a guidance document in which the FDA described its plans to conduct voluntary remote interactive evaluations of certain drug manufacturing facilities and clinical research sites, among other facilities. According to the guidance, the FDA may request such remote interactive evaluations where the FDA determines that remote evaluation would be appropriate based on mission needs and travel limitations. In May 2021, the FDA outlined a detailed plan to move toward a more consistent state of inspectional operations, and in July 2021, the FDA resumed standard inspectional operations of domestic facilities and was continuing to maintain this level of operation

as of September 2021. More recently, the FDA has continued to monitor and implement changes to its inspectional activities to ensure the safety of its employees and those of the firms it regulates as it adapts to the evolving COVID-19 pandemic. Regulatory authorities outside the United States have adopted 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 MHRA, 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, or any other product candidates in the EU and/or the United Kingdom. Although we have obtained FDA approval and marketing authorization from the European Commission and the MHRA for setmelanotide, any delay in obtaining, or an inability to obtain, any marketing authorization, for any of our other product candidates, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates 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 any of our other product candidates, 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 and foreign regulatory authorities, 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 foreign regulations, and are subject to FDA and foreign regulatory authorities 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 and foreign regulatory authorities also has the authority to require, as part of an NDA or similar foreign application or post approval, the submission of a REMS or other

specific obligations, which may include Elements to Assure Safe Use. Any REMS or other specific obligations required by the FDA or foreign regulatory authorities 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. Similar requirements apply in foreign jurisdictions.

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. 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 GMP 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 GMP. 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. Noncompliance 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 and elsewhere, 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, Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the ACA, was signed into law. 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," such as IMCIVREE, 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 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.

Since its enactment, certain provisions of the ACA have been subject to judicial, executive, and legislative challenges. On June 17, 2021, the U.S. Supreme Court dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the ACA. Prior to the Supreme Court's decision, President Biden issued an executive order initiating a special enrollment period from February 15, 2021 through August 15, 2021 for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare. It is unclear how healthcare reform measures enacted by Congress or implemented by the Biden administration or other challenges to the ACA, if any, will impact the ACA or our business.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. For example, beginning April 1, 2013, Medicare payments to providers were reduced by 2% under the sequestration required by the Budget Control Act of 2011, which will remain in effect through 2030, with the exception of a temporary suspension due to the COVID19 pandemic from May 1, 2020 through July 1, 2022 (with a 1% payment reduction from April 1 to June 30, 2022), unless additional Congressional action is taken. On January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, 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 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, drug price increase reporting, and other transparency measures. These types of initiatives may result in additional reductions in Medicare, Medicaid, and other healthcare funding, and may otherwise affect the prices we may obtain for IMCIVREE or the frequency with which IMCIVREE is prescribed or used.

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. For example, the Build Back Better

Act, if enacted, would introduce substantial drug pricing reforms, including the establishment of a drug price negotiation program within the U.S. Department of Health and Human Services that would require manufacturers to charge a negotiated "maximum fair price" for certain selected drugs or pay an excise tax for noncompliance, and the establishment of rebate payment requirements on manufacturers of certain drugs payable under Medicare Parts B and D. If the Build Back Better Act is not enacted, similar or other drug pricing proposals could appear in future legislation. 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 fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate Program or other governmental pricing programs in which we participate, 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.

Medicaid is a joint federal and state program administered by the states for low income and disabled beneficiaries. We participate in and have certain price reporting obligations under the Medicaid Drug Rebate Program, or the MDRP, as a condition of having covered outpatient drugs payable under Medicaid and, if applicable, under Medicare Part B. The MDRP requires us to pay a rebate to state Medicaid programs for each unit of our covered outpatient drugs dispensed to Medicaid beneficiaries and paid for by a state Medicaid program. These rebates are based on pricing data that we must report on a monthly and quarterly basis to the Centers for Medicare & Medicaid Services, or CMS, the federal agency that administers the MDRP and other governmental healthcare programs. These data include the average manufacturer price for each drug and, in the case of innovator products, the best price, which in general represents the lowest price available from the manufacturer to certain entities in the U.S. in any pricing structure, calculated to include all sales and associated rebates, discounts and other price concessions. If we become aware that our MDRP government price reporting submission for a prior quarter was incorrect or has changed as a result of recalculation of the pricing data, we must resubmit the corrected data for up to three years after those data originally were due. If we fail to provide information timely or are found to have knowingly submitted false information to the government, we may be subject to civil monetary penalties and other sanctions, including termination from the MDRP. In the event that CMS terminates our rebate agreement pursuant to which we participate in the MDRP, no federal payments would be available under Medicaid or Medicare Part B for our covered outpatient drugs. Our failure to comply with our MDRP price reporting and rebate payment obligations could negatively impact our financial results.

The ACA made significant changes to the MDRP, 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. In addition, in March 2021, the American Rescue Plan Act of 2021 was signed into law, which, among other things, eliminated the statutory cap on drug manufacturers' MDRP rebate liability, effective January 1, 2024. Under current law enacted as part of the ACA, drug manufacturers' MDRP rebate liability is capped at 100% of the average manufacturer price for a covered outpatient drug. Congress could enact additional legislation that further increases Medicaid drug rebates or other costs and charges associated with participating in the MDRP. Additional legislation or the issuance of regulations relating to the MDRP could have a material adverse effect on our results of operations.

Federal law requires that any company that participates in the MDRP also participate in the Public Health Service's 340B drug pricing program in order for federal funds to be available for the manufacturer's drugs under Medicaid and, if applicable, Medicare Part B. We participate in the 340B program, which is administered by the Health Resources and Services Administration, or HRSA, and requires us to charge statutorily defined covered entities no more than the 340B "ceiling price" for our 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," such as IMCIVREE, 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 MDRP, and in general, products subject to Medicaid price reporting and rebate liability are also subject to the 340B ceiling price calculation and discount requirement. We must report 340B ceiling prices to HRSA on a quarterly basis, and HRSA publishes those prices to 340B covered entities. In addition, HRSA has finalized regulations regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities for 340B-eligible drugs. HRSA has also finalized an administrative dispute resolution process through which 340B covered entities may pursue claims against participating manufacturers for overcharges, and through which manufacturers may pursue claims against 340B covered entities for engaging in unlawful diversion or duplicate discounting of 340B drugs. Our failure to comply 340B program requirements could negatively impact our financial results. 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 also negatively impact our financial results. In addition, legislation may be introduced that, if passed, would further expand the 340B program to additional covered entities or would require participating manufacturers to agree to provide 340B discounted pricing on drugs used in an inpatient setting.

In order 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 participate in the U.S. Department of Veterans Affairs, or VA, Federal Supply Schedule, or FSS, pricing program. As part of this program, we are required 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 must 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.

We also participate in the Tricare Retail Pharmacy program, under which we are 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 are 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 are 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.

Individual states continue to consider and have enacted legislation to limit the growth of healthcare costs, including the cost of prescription drugs and combination products. A number of states have either implemented or are considering implementation of drug price transparency legislation. Requirements of pharmaceutical manufacturers under such laws include advance notice of planned price increases, reporting price increase amounts and factors considered in taking such increases, wholesale acquisition cost information disclosure to prescribers, purchasers, and state agencies, and new product notice and reporting. Such legislation could limit the price or payment for certain drugs, and a number of states are authorized to impose civil monetary penalties or pursue other enforcement mechanisms against manufacturers who fail to comply with drug price transparency requirements, including the untimely, inaccurate, or incomplete reporting of drug pricing information.

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. CMS, the Department of Health & Human Services Office of Inspector General, and other governmental agencies have pursued manufacturers that were alleged to have failed to report these data to the government in a timely or accurate 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 MDRP, the 340B program, the VA/FSS program, the Tricare Retail Pharmacy Program, and other governmental drug pricing programs will not be found to be incomplete or incorrect.

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, state and foreign 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.

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, antikickback, 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, state and foreign 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. 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.

- 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.

- 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), certain non-physician practitioners (physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, anesthesiology assistants and certified nurse-midwives) and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. 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.

- Analogous foreign laws and regulations, including restrictions imposed on the promotion and marketing of medicinal products in the EU member states and other countries, 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, federal and foreign 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.

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.

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

The global data protection landscape is rapidly evolving, and we are or may become subject to numerous state, federal and foreign laws, requirements and regulations governing the collection, use, disclosure, retention, and security of

personal information. Implementation standards and enforcement practices are likely to remain uncertain for the foreseeable future, and we cannot yet determine the impact future laws, regulations, standards, or perception of their requirements may have on our business. This evolution may create uncertainty in our business, affect our ability to operate in certain jurisdictions or to collect, store, transfer use and share personal information, necessitate the acceptance of more onerous obligations in our contracts, result in liability or impose additional costs on us. The cost of compliance with these laws, regulations and standards is high and is likely to increase in the future. Any failure or perceived failure by us to comply with federal, state or foreign laws or regulations, our internal policies and procedures or our contracts governing our processing of personal information could result in negative publicity, government investigations and enforcement actions, claims by third parties and damage to our reputation, any of which could have a material adverse effect on our financial performance, business and operating results.

In the United States, numerous federal and state laws and regulations, including HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 and regulations implemented thereunder, collectively HIPAA, state data breach notification laws, state health information privacy laws and federal and state consumer protection laws, including Section 5 of the Federal Trade Commission Act, which govern the collection, use, disclosure and protection of health-related and other personal information, may apply to our operations and the operations of current and future collaborators. 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. Further, we may also be subject to other state laws governing the privacy, processing and protection of personal information. For example, the California Consumer Privacy Act of 2018, or CCPA, went into effect on January 1, 2020. The CCPA creates individual privacy rights for California consumers and increases the privacy and security obligations of entities handling certain personal information. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that is expected to increase data breach litigation. Further, the California Privacy Rights Act, or CPRA, recently passed in California. The CPRA will impose additional data protection obligations on covered businesses, including additional consumer rights processes, limitations on data uses, new audit requirements for higher risk data, and opt outs for certain uses of sensitive data. It will also create a new California data protection agency authorized to issue substantive regulations and could result in increased privacy and information security enforcement. The majority of the provisions will go into effect on January 1, 2023, and additional compliance investment and potential business process changes may be required. Similar laws have passed in Virginia and Colorado, and have been proposed in other states and at the federal level, reflecting a trend toward more stringent privacy legislation in the United States. The enactment of such laws could have potentially conflicting requirements that would make compliance challenging. In addition, 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. In the event that we are subject to or affected by HIPAA, the CCPA, the CPRA or other domestic privacy and data protection laws, any liability from failure to comply with the requirements of these laws could adversely affect our financial condition.

Furthermore, the Federal Trade Commission, or FTC, and many state Attorneys General continue to enforce federal and state consumer protection laws against companies for online collection, use, dissemination and security practices that appear to be unfair or deceptive. For example, according to the FTC, failing to take appropriate steps to keep consumers' personal information secure can constitute unfair acts or practices in or affecting commerce in violation of Section 5(a) of the Federal Trade Commission Act. The FTC expects a company's data security measures to be reasonable and appropriate in light of the sensitivity and volume of consumer information it holds, the size and complexity of its business, and the cost of available tools to improve security and reduce vulnerabilities.

Our operations abroad may also be subject to increased scrutiny or attention from data protection authorities. For example, in Europe, the collection and use of personal data, including health and genetic data, is governed by the provisions of the GDPR. The GDPR became effective on May 25, 2018, and imposes strict requirements for the processing of the personal data of individuals within the European Economic Area, or EEA, including health data from clinical trials and AE reporting. In particular, these requirements include certain obligations 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, and security and confidentiality of the personal data, and violations of these requirements could result in substantial fines, 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. Data protection authorities from the different EU and EEA member states may also interpret the GDPR and national laws differently and impose additional requirements, which adds to the complexity of processing personal data in the EU and the EEA.

Additionally, from January 1, 2021, we have had to comply with the GDPR and also the United Kingdom GDPR, or UK GDPR, which, together with the amended United Kingdom Data Protection Act 2018, retains the GDPR in United Kingdom national law following Brexit. The UK 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 EU 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.

Among other requirements, the GDPR and UK GDPR also regulate transfers of personal data subject to the GDPR to third countries that have not been found to provide adequate protection to such personal data, including the United States; in July, 2020, the Court of Justice of the European Union, or the CJEU, invalidated the EU-US Privacy Shield Framework, or the Privacy Shield, under which personal data could be transferred from the EEA to US entities who had self-certified under the Privacy Shield scheme and imposed further restrictions on the use of the standard contractual clauses, or SCCs. These restrictions include a requirement for companies to carry out a transfer impact assessment which, among other things, assesses the laws governing access to personal data in the recipient country and considers whether supplementary measures that provide privacy protections additional to those provided under SCCs will need to be implemented to ensure an essentially equivalent level of data protection to that afforded in the EEA. The European Commission issued revised SCCs on June 4, 2021 to account for the decision of the CJEU and recommendations made by the European Data Protection Board. The revised SCCs must be used for relevant new data transfers from September 27, 2021; existing standard contractual clauses arrangements must be migrated to the revised clauses by December 27, 2022. There is some uncertainty around whether the revised clauses can be used for all types of data transfers, particularly whether they can be relied on for data transfers to non-EEA entities subject to the GDPR. The revised SCCs apply only to the transfer of personal data outside of the EEA and not the United Kingdom; the UK's Information Commissioner's Office launched a public consultation on its draft revised data transfers mechanisms in August 2021. 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. The European Commission has adopted an adequacy decision in favor of the United Kingdom, enabling data transfers from EU member states to the United Kingdom without additional safeguards. However, the UK adequacy decision will automatically expire in June 2025 unless the European Commission re-assesses and renews/extends that decision, and remains under review by the European Commission during this period. The relationship between the United Kingdom and the EU 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, and how data transfers to and from the United Kingdom will be regulated in the long term.

Although we work to comply with applicable laws, regulations and standards, our contractual obligations and other legal obligations, these requirements are evolving and may be modified, interpreted and applied in an inconsistent manner from one jurisdiction to another, and may conflict with one another or other legal obligations with which we must comply. 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. And any actual or perceived

failure to comply with these data protection laws or adequately address privacy and security concerns could lead to government enforcement actions and significant penalties against us, and adversely impact our operating results.

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, including RareStone. If we commercialize setmelanotide in foreign markets, we will be subject to additional risks and uncertainties, including:

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

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

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

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

Compliance with the FCPA is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the FCPA presents particular challenges in the pharmaceutical industry, because, in many countries, hospitals are operated by the government, and doctors and other hospital employees are considered foreign officials.

Certain payments to hospitals in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions.

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

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

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

Following a national referendum and enactment of legislation by the government of the United Kingdom, the United Kingdom formally withdrew from the EU on January 31, 2020 and ratified a trade and cooperation agreement governing its future relationship (commonly referred to as "Brexit"). The agreement, which was applied provisionally from January 1, 2021 and entered into force on May 1, 2021, addresses trade, economic arrangements, law enforcement, judicial cooperation and a governance framework including procedures for dispute resolution, among other things. Because the agreement merely sets forth a framework in many respects and will require complex additional bilateral negotiations between the United Kingdom and the EU as both parties continue to work on the rules for implementation, significant political and economic uncertainty remains about how the precise terms of the relationship between the parties will differ from the terms before withdrawal.

Since January 1, 2021, however, the United Kingdom operates under a separate regulatory regime to the EU. EU laws regarding medicinal products only apply in respect of the United Kingdom to Northern Ireland (as set out in the Protocol on Ireland/Northern Ireland). The EU laws that have been transposed into United Kingdom law through secondary legislation remain applicable. While the United Kingdom has indicated a general intention that new laws regarding the development, manufacture and commercialisation of medicinal products in the United Kingdom will align closely with EU law, there are limited detailed proposals for future regulation of medicinal products. The trade and cooperation agreement includes specific provisions concerning medicinal products, which include the mutual recognition of GMP, inspections of manufacturing facilities for medicinal products and GMP documents issued (such mutual recognition can be rejected by either party in certain circumstances), but does not foresee wholesale mutual recognition of United Kingdom and EU pharmaceutical regulations. For example, it is not clear to what extent the United Kingdom will adopt legislation aligned with, or similar to, the EU CTR which became applicable on January 31, 2022 and which significantly reforms the assessment and supervision processes for clinical trials throughout the EU. Therefore, there remains political and economic uncertainty regarding to what extent the regulation of medicinal products will differ between the United Kingdom and the EU in the future. Any divergences will increase the cost and complexity of running our business, including with respect to the conduct of clinical trials. Brexit also materially impacted the regulatory regime with respect to the approval of our product candidates. Great Britain is no longer covered by the EU's procedures for the grant of marketing authorizations (Northern Ireland is covered by the centralized authorisation procedure and can be covered under the decentralized or mutual recognition procedures). As of January 1, 2021, all existing centralized marketing authorizations were automatically converted into United Kingdom marketing authorizations effective in Great Britain and issued with a United Kingdom marketing authorization number on January 1, 2021 (unless marketing authorization holders opted out of this scheme). A separate marketing authorization is now required to market drugs in Great Britain. It is currently unclear whether the regulator in the United Kingdom, the MHRA is sufficiently prepared to handle the increased volume of marketing authorisation applications that it is likely to receive. Any delay in obtaining, or an inability to obtain, any regulatory approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in Great Britain and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in Great Britain for our product candidates,

which could significantly and materially harm our business. 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.

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 11.9% of our outstanding voting stock as of December 31, 2021. 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 or EMA to approve IMCIVREE for additional indications;
- 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, 2021, we had approximately $422.3 million and $385.1 million of unused federal and state NOL carryforwards, respectively, and approximately $9.3 million and $4.2 million of unused federal and state carryforwards of research tax credits, respectively. Of the federal NOL carryforwards at December 31, 2021, $349.2 million can be carried forward indefinitely, while $73.2 million will begin to expire in 2033. Additionally, as of December 31, 2021, we had federal orphan drug credits related to qualifying research of $15.4 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, 2021, we had 50,283,574 shares of common stock outstanding.

The holders of an aggregate of approximately 5.9 million shares of our common stock, or approximately 11.9% of our total outstanding common stock as of December 31, 2021, 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.

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, 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.

The increasing focus on environmental sustainability and social initiatives could increase our costs, harm our reputation and adversely impact our financial results.

There has been increasing public focus by investors, customers, environmental activists, the media and governmental and nongovernmental organizations on a variety of environmental, social and other sustainability matters. We experience pressure to make commitments relating to sustainability matters that affect us, including the design and implementation of specific risk mitigation strategic initiatives relating to sustainability. If we are not effective in addressing environmental, social and other sustainability matters affecting our business, or setting and meeting relevant sustainability goals, our reputation and financial results may suffer. We may experience increased costs in order to execute upon our sustainability goals and measure achievement of those goals, which could have a materially adverse impact on our business and financial condition.

In addition, this emphasis on environmental, social and other sustainability matters has resulted and may result in the adoption of new laws and regulations, including new reporting requirements. If we fail to comply with new laws, regulations or reporting requirements, our reputation and business could be adversely impacted.

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 5 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 we may 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 22, 2022, 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.

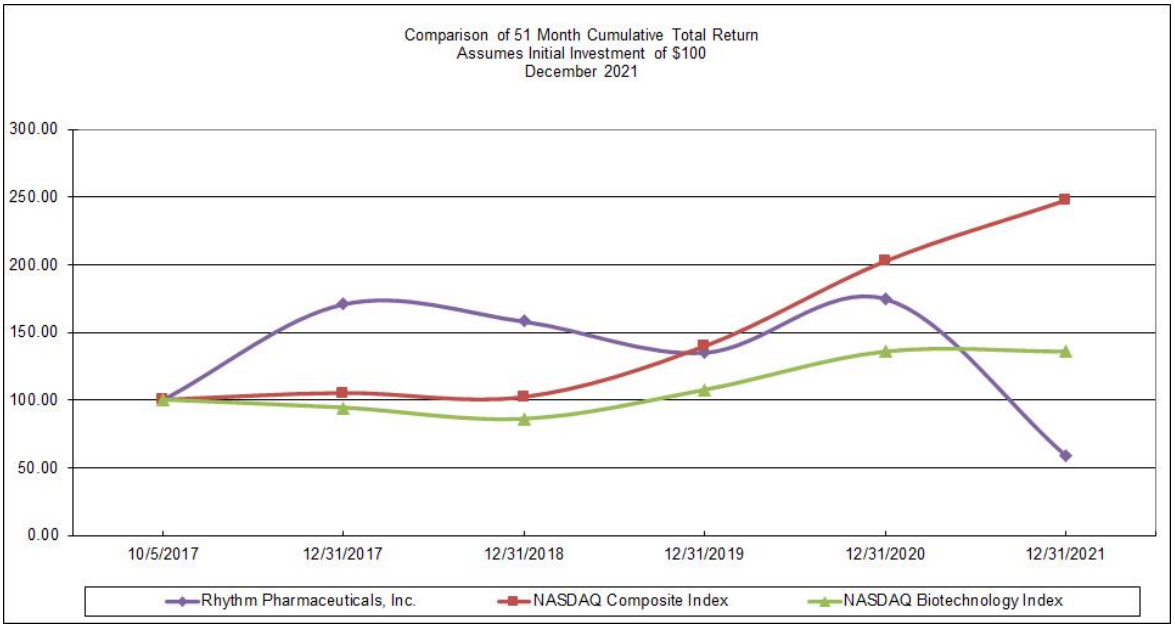
Dividend Policy

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, 2021 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. [Reserved]

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 2020 fiscal year specifically, as well as the year-over-year comparison of our 2020 financial performance to 2019, 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, 2020, filed with the SEC on March 1, 2021.

Overview

We are a global, 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 hyperphagia, a pathological and insatiable hunger. While obesity affects hundreds of millions of people worldwide, we are advancing IMCIVREE™ (setmelanotide) as a precision medicine strategy for a subset of individuals who have severe obesity due to genetic variants that impair the melanocortin-4 receptor (MC4R) pathway, a pathway in the brain that is responsible for regulating hunger, caloric intake and energy expenditure, which consequently affect body weight. IMCIVREE, an MC4R agonist for which we hold worldwide rights, is the first-ever therapy developed for patients with certain ultra-rare genetic diseases of obesity that is approved or authorized in the United States, European Union (EU) or Great Britain. We made IMCIVREE commercially available in the United States for patients 6 years and older with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency in early 2021, and we are working to achieve market access in several European countries in 2022. In addition to initial commercial efforts, we are preparing to bring IMCIVREE to additional populations in 2022 and beyond. We are advancing a broad clinical development program for setmelanotide in patients with additional rare genetic diseases of obesity 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.

IMCIVREE was approved in November 2020 by the U.S. Food and Drug Administration (FDA) 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. The European Commission (EC) and Great Britain's Medicines & Healthcare Products Regulatory Agency (MHRA), in July and September 2021, respectively, granted marketing authorization to IMCIVREE for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. These approvals were based on Phase 3 data demonstrating a statistically significant and clinically meaningful reduction of weight and hunger in patients 12 years old or older with severe obesity due to POMC, PCSK1 or LEPR deficiency. In addition to the United States and Europe/UK, we and our partners are seeking approval for IMCIVREE to treat patients with these genetic obesities in Israel, China, Hong Kong and Macau.

Additionally, we are seeking regulatory approvals in the United States and Europe for setmelanotide to treat obesity and control hunger in patients with Bardet-Biedl syndrome (BBS) or Alström syndrome. In November 2021, we announced the U.S. FDA has accepted for filing our supplemental New Drug Application (sNDA) for setmelanotide seeking to expand the approved label to include patients with BBS or Alström syndrome and granted us priority review for this sNDA. The FDA has assigned a Prescription Drug User Fee Act (PDUFA) goal date of June 16, 2022 for this sNDA. In October 2021, we announced that we submitted a Type II variation application to the European Medicines Agency (EMA) for setmelanotide for the treatment of obesity and control of hunger in adult and pediatric patients 6 years of age and older with BBS or Alström syndrome. These regulatory submissions are based on positive results from a pivotal Phase 3 clinical trial that met its primary and all key secondary endpoints and achieved clinically meaningful and statistically significant reductions in body weight and in hyperphagia associated with these syndromes. The submissions include a series of comprehensive individual patient narratives supporting the disease burden of BBS. Our belief is that setmelanotide, if approved, has the potential to offer the first therapeutic option for the early-onset, severe obesity and unrelenting hunger that characterize these syndromes. Recently, we have decided to withdraw the Alström syndrome indication from the pending Type II variation application based on feedback from the EMA.

We also are advancing a broad clinical development program evaluating setmelanotide in several ongoing and planned clinical trials, and we are leveraging what we believe is the largest known DNA database focused on obesity -

with approximately 45,000 sequencing samples as of December 31, 2021 - to improve the understanding, diagnosis and care of people living with severe obesity due to certain variants in genes associated with the MC4R pathway. Having achieved proof-of-concept in our ongoing exploratory Phase 2 Basket Study evaluating setmelanotide in patients with severe obesity driven by variants in several different MC4R pathway associated genes, we expect to initiate in the first half of 2022, the pivotal Phase 3 EMANATE clinical trial, a randomized, double-blind, placebo-controlled to evaluate setmelanotide in five independent sub-studies in patients with obesity due to a heterozygous variant of the POMC/PCSK1 genes or LEPR gene, certain rare variants of the SRC1 gene or the SH2B1 gene, or the N221D variant in the PCSK1 gene. We also have initiated the Phase 2 DAYBREAK clinical trial designed to evaluate setmelanotide in patients who carry a confirmed variant in one or more of 31 additional genes with strong or very strong relevance to the MC4R pathway. Our broad clinical program evaluating setmelanotide in rare diseases of obesity also includes the ongoing exploratory Phase 2 Basket study, an ongoing Phase 2 study evaluating setmelanotide in patients with hypothalamic obesity, a Phase 3 study in pediatric patients with MC4R pathway deficiencies between the ages of 2 and 6 years old, and potential registration-enabling study with our once-weekly formulation of setmelanotide.

We are studying additional diseases as part of investigator-initiated protocols. There are currently no effective or approved treatments for these MC4R pathway-related diseases. 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.

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.

On November 2, 2021, we entered into a sales agreement, or the Sales Agreement, with Cowen and Company LLC, or Cowen, as sales agent, pursuant to which we may, from time to time, issue and sell common stock with an aggregate value of up to $100 million in "at-the-market" offerings, or the ATM, under our Registration Statement on Form S-3 (File No. 333-260689) filed with the SEC on November 2, 2021. Sales of common stock, if any, pursuant to the Sales Agreement, may be made in sales deemed to be an “at the market offering” as defined in Rule 415(a) of the Securities Act, including sales made directly through The Nasdaq Global Market or on any other existing trading market for our common stock. During the year ended December 31, 2021, did not sell any shares of common stock under the Sales Agreement. As of December 31, 2021, there was $100.0 million of common stock remaining available for sale under the ATM.

Our operations to date have been limited primarily to conducting research and development activities for setmelanotide. To date, we have not generated any significant 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. As noted above, we also received $100.0 million from an asset sale, specifically in connection with the PRV Transfer. In December 2021, we entered into an Exclusive License Agreement with RareStone Group Ltd., and received $7.0 million from the execution of that agreement.

We will not generate significant revenue from product sales until we are able to successfully establish a marketing and commercialization infrastructure for IMCIVREE. IMCIVREE became 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 and following marketing authorizations in the European Union and Great Britain, we are pursuing a country-by-country strategy to establish market access and reimbursement for IMCIVREE in several countries. 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 collaboration or out license arrangements 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, 2021 we had an accumulated deficit of $528.9 million. Our net losses were $69.6 million and $134.0 million, for the years ended December 31, 2021 and 2020, 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;
- engage in the sales and marketing efforts necessary to support the continued commercial efforts of IMCIVREE globally;
- take into account the levels, timing and collection of revenue earned from sales of IMCIVREE and other products approved in the future, if any; and
- continue to operate as a public company.

As of December 31, 2021, our cash and cash equivalents and short-term investments were approximately $294.9 million. We expect that our cash and cash equivalents and short-term investments as of December 31, 2021, will enable us to fund our operating expenses into 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. Based on current information we do not currently anticipate any disruption in the clinical supply of setmelanotide. 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 duration of the pandemic, the impact of variants, 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 significant revenue from product sales. Our lead product candidate, IMCIVREE, was approved by the FDA in November 2020 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. IMCIVREE became commercially available in the U.S. in the first quarter of 2021. We recorded our first sales of IMCIVREE in March 2021. We expect our initial sales of IMCIVREE will be limited by the ultra-rare nature of the disease and limited number of diagnosed patients in the United States.

Cost of sales

All of our inventory of IMCIVREE produced prior to FDA approval is available for commercial or clinical use. Most of the manufacturing costs have been recorded as research and development expenses in prior periods. Accordingly, the costs for IMCIVREE included in our cost of sales for the year ended December 31, 2021 were insignificant. We expect cost of sales to increase in 2022 as we began to sell inventory that is produced after we began capitalizing IMCIVREE commercial inventory.

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:

	December 31,	
Research and development summary	**2021**	**2020**
Research and development expense	$ 104,128	$ 90,450

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.

Selling, general and administrative summary	December 31, 2021	2020
Selling, general and administrative expense	$ 68,486	$ 46,125

We anticipate that our selling, general and administrative expenses will increase in the future to support continued and expanding business support needs, commercialization for IMCIVREE in the United States and the European Union as well as other international markets as well as increased costs of operating as a global commercial stage biopharmaceutical 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, 2021, we had reserved 8,994,352 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, 2021, 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, 2021, we had net operating loss carryforwards to reduce federal and state incomes taxes of approximately $429.3 million and $392.0 million, respectively. If not utilized, these carryforwards begin to expire in 2033. Of the federal net operating loss carryforwards at December 31, 2021, $356.2 million can be carried forward indefinitely. At December 31, 2021, we also had available research and development tax credits for federal and state income tax purposes of approximately $9.3 million and $3.9 million, respectively. Additionally, as of December 31, 2021, we had federal orphan drug credits related to qualifying research of $15.4 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, 2021 and 2020.

The following table summarizes our results of operations for the years ended December 31, 2021 and 2020, together with the changes in those items in dollars and as a percentage:

	Year Ended December 31,		Change	
	2021	2020	$	%
	(in thousands)			
Statement of Operations Data:				
Product Revenue, net	$ 3,154	$ —	$ 3,154	NM
Costs and expenses:				
Cost of sales	599	—	599	NM
Research and development	104,128	90,450	13,678	15 %
Selling, general, and administrative	68,486	46,125	22,361	48 %
Total costs and expenses	173,213	136,575	36,638	27 %
Loss from operations	(170,059)	(136,575)	(33,484)	25 %
Other income, net	100,447	2,579	97,868	3,795 %
Net loss	$ (69,612)	$ (133,996)	$ 64,384	(48)%

NM=Not meaningful

Product revenue, net increased to $3.2 million in 2021. There were no product revenues in the comparative prior period. We recorded our first sales of IMCIVREE in March 2021 and the year ended December 31, 2021 represents our first year of sales subsequent to the approval of IMCIVREE in November 2020. We expect our initial sales of IMCIVREE will be limited by the ultra-rare nature of the disease and limited number of diagnosed patients in the United States. To date, all of our product revenue has been generated in the United States.

Cost of sales increased to $0.6 million in 2021. There were no cost of sales in the comparative prior period. All of our inventory of IMCIVREE produced prior to FDA approval is available for commercial or clinical use. Most of the manufacturing costs have been recorded as research and development expenses in prior periods. Accordingly, the costs for IMCIVREE included in our cost of sales for the year ended December 31, 2021 were insignificant and primarily reflect the amortization of our capitalized sales based milestone payment made to Ipsen upon our first commercial sale as well as a royalty due to Ipsen on our net product sales. We expect cost of sales to increase as we begin to sell inventory that is produced after we began capitalizing IMCIVREE commercial inventory.

Research and development expense. Research and development expense increased by $13.7 million to $104.1 million in 2021 from $90.5 million in 2020, an increase of 15%. The increase was primarily due to the following:

- an increase of $11.2 million in our clinical trial costs associated with new and planned clinical trials, including our Phase 2 DAYBREAK and Phase 3 EMANATE trials, Phase 3 pediatrics trial, QTc study, Phase 2 hypothalamic obesity study, and increased enrollment in our long-term extension study. These increases were partially offset by the conclusion of prior studies, including pivotal Phase 3 studies for POMC and LEPR, as well as GO-ID;

- an increase of $7.7 million in salaries, benefits and stock-based compensation related to the hiring of additional full-time employees in order to support the growth of our research and development programs; and

- an increase of $1.3 million of pre-clinical expenses associated with second generation drug development.

The above increases were partially offset by:

- a decrease 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;
- a decrease of $2.0 million primarily related to purchases of setmelanotide API and drug product for clinical trials and preparation for potential commercialization; and
- a decrease of $1.4 million in costs associated with accessing sequencing data from third-party biobanks to further our genetic research efforts.

Selling, general and administrative expense. Selling, general and administrative expense increased by $22.4 million to $68.5 million in 2021 from $46.1 million in 2020, an increase of 48%. The increase was primarily due to the following:

- an increase of $9.9 million due to increased compensation and benefits related costs associated with additions to our executive leadership team, increased headcount to support our expanding business operations as well as to establish commercial operations in the United States and internationally;
- an increase of $5.9 million due to increased professional fees and consulting services to support the build out of our commercial operations in the United States and internationally as well as corporate legal and consulting support for our international expansion;
- an increase of $3.7 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.;
- an increase of $1.6 million of fees associated with the sale of our PRV to Alexion; and
- and increase of $1.3 million of employee recruitment and other missellaneous office related expenses to support our expanding business operations in the United States and internationally.

Liquidity and Capital Resources

As of December 31, 2021, our cash and cash equivalents and short-term investments were approximately $294.9 million.

Cash flows

The following table provides information regarding our cash flows for the years ended December 31, 2021 and 2020:

	Year Ended December 31,	
	2021	2020
	(in thousands)	
Net cash provided by (used in):		
Operating activities	$ (146,003)	$ (121,980)
Investing activities	(62,159)	158,531
Financing activities	166,481	2,009
Net (decrease) increase in cash, cash equivalents and restricted cash	$ (41,681)	38,560

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 $146.0 million for the year ended December 31, 2021, and consisted primarily of a net loss of $147.9 million adjusted for non-cash items, which consisted of the gain on the sale of the PRV, non-cash stock-based compensation, depreciation and amortization and rent expense. The change in operating assets and liabilities reflected a total source of cash of approximately $1.9 million primarily driven by an increase in accounts payable and accrued expenses of $18.3 million due to the timing of payments, partially offset by an increase of $16.4 million in prepaid expenses, other current and other long term assets.

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 an increase in prepaid assets, accounts payable and accrued expenses due to the timing of payments and an increase in overall operating expenses.

Net cash provided by (used in) investing activities

Net cash used in investing activities was $62.2 million for the year ended December 31, 2021 which relates to the purchases of short-term investments, net of maturities, of $163.7 million, $0.4 million related to the purchase of property plant and equipment and $5.0 million for the acquisition of an intangible asset, partially offset by the $100.0 million in proceeds from the sale of the PRV and $7.0 million in proceeds from an out-license agreement.

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 provided by financing activities

Net cash provided by financing activities was $166.5 million for the year ended December 31, 2021, which represents the net proceeds of $161.7 million from our common stock offering in February 2021 and $4.8 million of cash proceeds from the exercise of stock options and the issuance of common stock from our 2017 Employee Stock Purchase Plan, or the ESPP.

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.

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 $294.9 million of cash and cash equivalents and short-term investments as of December 31, 2021, will enable us to fund our operating expenses into 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 became 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 and at December 31, 2021 there were $31.0 million of remaining milestones that may be achieved and due to Ipsen at a future date. We expect to pay Ipsen a $4.0 million milestone in 2022 upon our first commercial sale of IMCIVREE in the Europe. 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 and at December 31, 2021 there were $63.5 million of remaining milestones that may be achieved and due to Camurus at a future date. We expect to pay Camurus a $1.0 million milestone in 2022 upon the achievement of a development milestone. 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, 2021, potential payments due to third parties, during the next 12 months from the filing of this Annual Report are estimated to be approximately $5.0 million in commercial and development 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.

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, 2021, 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, 2021. 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, 2021. 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 2021 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, 2021, 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, 2021, 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, 2021 and 2020, 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, 2021, and the related notes and our report dated March 1, 2022 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, 2022

Item 9B. Other Information

None

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections.

Not applicable.

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 2022 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, 2021.

Item 11. Executive Compensation

The information required under this item is incorporated herein by reference to our definitive proxy statement for our 2022 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, 2021.

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, 2021, 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	7,129,333	$ 21.84	1,865,019
2017 ESPP	—	—	962,942
Equity compensation plans not approved by stockholders	—	—	—
Total	7,129,333	$ 21.84	2,827,961

(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 2022 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, 2021.

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 2022 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, 2021.

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 2022 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, 2021.

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
4.2.1	Amended and Restated Investors' Rights Agreement, dated August 21, 2017.	S-1	9/5/2017	4.2
4.2.2	Amendment No. 1 to Amended and Restated Investors' Rights Agreement, dated January 25, 2021.	10-Q	11/02/2021	4.1
4.3	Form of Indenture to be entered into between the Registrant and a trustee acceptable to the registrant.	S-3	11/2/2021	4.3
4.4	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
10.5.1†*	2022 Employment Inducement Plan and Form of Option Agreement			
10.5.2†*	2022 Employment Inducement Plan Form of Restricted Stock Unit Agreement			
10.6†*	Summary of Non-Employee Director Compensation Policy			
10.7‡	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
10.8‡	License Agreement, dated January 4, 2016, by and between the Registrant and Camurus AB.	S-1	9/5/2017	10.8
10.9‡	License Agreement, dated March 30, 2018, by and between the Registrant and Takeda Pharmaceutical Company Limited.	10-Q	5/14/2018	10.1
10.10‡‡*	License Agreement, dated December 3, 2021, by and between the Registrant and RareStone Group Ltd.			
10.11.1‡	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
10.12.2‡	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

10.13.3‡	Second Amendment to Development and Manufacturing Services Agreement, dated July 15, 2020, by and between the Registrant and Corden Pharma Brussels S.A.	10-Q	8/3/2020	10.1
10.14	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
10.15.1	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
10.16.2	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
10.17.3	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
10.18†	Offer Letter, dated December 21, 2017, by and between the Registrant and Hunter Smith.	10-Q	5/4/2020	10.2
10.19†	Offer Letter, dated September 4, 2020, by and between the Registrant and Yann Mazabraud.	10-Q	11/2/2020	10.1
10.20†	Offer Letter, dated May 10, 2018, by and between the Registrant and Simon D. Kelner.	10-K	3/1/2021	10.15
10.21.1†	Offer Letter, dated September 14, 2018, by and between the Registrant and Murray Stewart M.D.	10-K	3/1/2021	10.15
10.21.2†*	Consulting Agreement, dated September 11, 2021, by and between the Registrant and Murray Stewart, D.M., F.R.C.P.			
10.22†	Offer Letter, dated September 25, 2020, by and between the Registrant and Jennifer Chien.	10-K	3/1/2021	10.16
10.23†	Offer Letter, dated July 16, 2020, by and between the Registrant and David P. Meeker M.D.	8-K	7/21/2020	10.1
10.24†	Offer Letter, dated July 9, 2021, by and between the Registrant and Pamela Cramer	10-Q	08/03/2021	10.1
10.25†	Offer Letter, dated September 1, 2021, by and between the Registrant and Linda Shapiro Manning, M.D.	10-Q	11/02/2021	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.

‡‡ Indicates that portions of this exhibit (indicated by asterisks) have been omitted pursuant to Regulation S-K, Item 601(b)(10). Such omitted information is not material and the registrant customarily and actually treats such information as private or confidential.

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, 2022
/s/ Hunter Smith Hunter Smith	Chief Financial Officer (Principal Financial Officer)	March 1, 2022
/s/ William T. Roberts William T. Roberts	Chief Accounting Officer (Principal Accounting Officer)	March 1, 2022
/s/ Edward T. Mathers Edward T. Mathers	Lead Director	March 1, 2022
/s/ Stuart Arbuckle Stuart Arbuckle	Director	March 1, 2022
/s/ Camille L. Bedrosian, M.D. Camille L. Bedrosian M.D.	Director	March 1, 2022
/s/ Jennifer L. Good Jennifer L. Good	Director	March 1, 2022
/s/ Christophe R. Jean Christophe R. Jean	Director	March 1, 2022
/s/ David W. J. McGirr David W. J. McGirr	Director	March 1, 2022
/s/ Lynn A. Tetrault Lynn A. Tetrault	Director	March 1, 2022

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, 2021 and 2020, 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, 2021, 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, 2021 and 2020, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2021, 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, 2021, 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, 2022 expressed an unqualified opinion thereon.

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 $30.1 million at December 31, 2021, which included the estimated obligation for research and development expenses incurred as of December 31, 2021 but not paid as of that date. In addition, the Company's total prepaid expenses and other current assets were $12.5 million and other long-tem assets were $11.8 million at December 31, 2021, 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, 2021 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, 2022

RHYTHM PHARMACEUTICALS, INC.

CONSOLIDATED BALANCE SHEETS

(in thousands, except share and per share data)

	December 31, 2021	December 31, 2020
Assets		
Current assets:		
Cash and cash equivalents	$ 59,248	$ 100,854
Short-term investments	235,607	71,938
Accounts receivable	1,025	—
Prepaid expenses and other current assets	12,507	8,876
Total current assets	308,387	181,668
Property and equipment, net	2,813	3,195
Right-of-use asset	1,522	1,807
Intangible assets, net	4,658	—
Restricted cash	328	403
Other long-term assets	11,815	—
Total assets	$ 329,523	$ 187,073
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 5,737	$ 4,900
Accrued expenses and other current liabilities	30,084	12,559
Contract liability	7,000	—
Lease liability	606	535
Total current liabilities	43,427	17,994
Long-term liabilities:		
Lease liability	1,945	2,551
Total liabilities	45,372	20,545
Commitments and contingencies (Note 10)		
Stockholders' equity:		
Preferred Stock, $0.001 par value: 10,000,000 shares authorized; no shares issued and outstanding at December 31, 2021 and December 31, 2020	—	—
Common stock, $0.001 par value: 120,000,000 shares authorized; 50,283,574 and 44,235,903 shares issued and outstanding at December 31, 2021 and December 31, 2020, respectively	50	44
Additional paid-in capital	813,041	625,762
Accumulated other comprehensive (loss) income	(1)	49
Accumulated deficit	(528,939)	(459,327)
Total stockholders' equity	284,151	166,528
Total liabilities and stockholders' equity	$ 329,523	$ 187,073

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, 2021	Year Ended December 31, 2020	Year Ended December 31, 2019
Product revenue, net	$ 3,154	$ —	$ —
Costs and expenses:			
Cost of sales	599	—	—
Research and development	104,128	90,450	109,450
Selling, general, and administrative	68,486	46,125	36,550
Total costs and expenses	173,213	136,575	146,000
Loss from operations	(170,059)	(136,575)	(146,000)
Other income:			
Other income	100,000	—	—
Interest income, net	447	2,579	5,271
Total other income, net	100,447	2,579	5,271
Net loss	$ (69,612)	$ (133,996)	$ (140,729)
Net loss per share, basic and diluted	(1.40)	(3.04)	(3.86)
Weighted-average common shares outstanding, basic and diluted	49,600,294	44,127,220	36,422,450
Other comprehensive loss:			
Net loss	$ (69,612)	$ (133,996)	$ (140,729)
Unrealized (loss) gain on marketable securities	(1)	49	144
Comprehensive loss	$ (69,613)	$ (133,947)	$ (140,585)

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 (Loss)	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balance at December 31, 2018	34,410,725	34	430,824	—	(184,602)	246,256
Stock compensation expense	—	—	11,875	—	—	11,875
Issuance of common stock in connection with ESPP	25,871	—	558	—	—	558
Issuance of common stock in connection with exercise of stock options	235,833	1	1,563	—	—	1,564
Issuance of common stock upon completion of public offering, net of offering costs	9,324,324	9	161,343	—	—	161,352
Change in unrealized gain on marketable securities	—	—	144	—	—	144
Net loss	—	—	—	—	(140,729)	(140,729)
Balance at December 31, 2019	43,996,753	$ 44	$ 606,307	$ —	$ (325,331)	$ 281,020
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	209,098	—	1,478	—	—	1,478
Change in 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
Stock compensation expense	—	—	20,804	—	—	20,804
Issuance of common stock in connection with ESPP	38,051	—	621	—	—	621
Issuance of common stock in connection with exercise of stock options and vesting of restricted stock units	259,620	—	4,134	—	—	4,134
Issuance of common stock upon completion of public offering, net of offering costs	5,750,000	6	161,720	—	—	161,726
Unrealized loss on marketable securities	—	—	—	(50)	—	(50)
Net loss	—	—	—	—	(69,612)	(69,612)
Balance at December 31, 2021	50,283,574	$ 50	$ 813,041	$ (1)	$ (528,939)	$ 284,151

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,	
	2021	2020
Operating activities		
Net loss	$ (69,612)	$ (133,996)
Adjustments to reconcile net loss to net cash used in operating activities:		
Stock-based compensation expense	20,804	17,455
Gain on sale of priority review voucher	(100,000)	—
Depreciation and amortization	1,158	690
Non-cash rent expense	(250)	(234)
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	(4,600)	551
Other long-term assets	(11,815)	—
Accounts payable, accrued expenses and other current liabilities	18,312	(6,446)
Net cash used in operating activities	(146,003)	(121,980)
Investing activities		
Purchases of short-term investments	(524,972)	(86,869)
Maturities of short-term investments	361,247	245,614
Proceeds from sale of priority review voucher	100,000	—
Proceeds from out-license agreement	7,000	—
Milestone obligation under license agreement	(5,000)	—
Purchases of property and equipment	(434)	(214)
Net cash (used in) provided by investing activities	(62,159)	158,531
Financing activities		
Net proceeds from issuance of common stock	161,726	—
Proceeds from the exercise of stock options	4,134	1,487
Proceeds from issuance of common stock from ESPP	621	522
Net cash provided by financing activities	166,481	2,009
Net (decrease) increase in cash, cash equivalents and restricted cash	(41,681)	38,560
Cash, cash equivalents and restricted cash at beginning of period	101,257	62,697
Cash, cash equivalents and restricted cash at end of period	$ 59,576	$ 101,257

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 global, 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 hyperphagia, a pathological and insatiable hunger. While obesity affects hundreds of millions of people worldwide, we are advancing IMCIVREE™ (setmelanotide) as a precision medicine strategy for a subset of individuals who have severe obesity due to genetic variants that impair the melanocortin-4 receptor (MC4R) pathway, a pathway in the brain that is responsible for regulating hunger, caloric intake and energy expenditure, which consequently affect body weight. IMCIVREE, an MC4R agonist for which we hold worldwide rights, is the first-ever therapy developed for patients with certain ultra-rare genetic diseases of obesity that is approved or authorized in the United States, European Union (EU) or Great Britain. We made IMCIVREE commercially available in the United States for patients 6 years and older with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency in early 2021, and we are working to achieve market access in several European countries in 2022. In addition to initial commercial efforts, we are preparing to bring IMCIVREE to additional populations in 2022 and beyond. We are advancing a broad clinical development program for setmelanotide in patients with additional rare genetic diseases of obesity in an effort to expand the approved indications in the United States and Europe.

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 has wholly owned subsidiaries in the US, Ireland, the United Kindgdom and the Netherlands.

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.

There are many uncertainties regarding the COVID-19 pandemic, and the Company is closely monitoring the impact of the pandemic on all aspects of its business, including how the pandemic will impact its patients, employees, suppliers, vendors, business partners and distribution channels. While the pandemic did not materially affect the Company's financial results and business operations for the twelve months ended December 31, 2021, the Company is unable to predict the impact that COVID-19 will have on its financial position and operating results in future periods due to numerous uncertainties. The Company will continue to assess the evolving impact of the COVID-19 pandemic and will make adjustments to its operations as necessary.

Liquidity

The Company has incurred operating losses and negative cash flows from operations since inception. As of December 31, 2021, the Company had an accumulated deficit of $528,939. The Company has primarily funded these

losses through the proceeds from the sales of common and preferred stock, asset sales, outlicensing the rights to IMCIVREE in certain markets, as well as capital contributions received from the former parent company, Rhythm Holdings LLC. To date, the Company has minimal 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.

In February 2021, the Company completed the sale of a Rare Pediatric Disease Priority Review Voucher, or PRV, that it received in connection with the approval of IMCIVREE for $100,000. As the PRV did not have a carrying value, the gain recognized within Other income (loss) was equal to the gross proceeds received, with costs related to the sale of the voucher recorded within selling, general and administrative expenses. Additionally in February 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 offering expenses. 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 November 2021, the Company entered into a sales agreement, or the Sales Agreement, with Cowen and Company LLC, or Cowen, as sales agent, pursuant to which the Company may, from time to time, issue and sell common stock with an aggregate value of up to $100 million in "at-the-market" offerings, or the ATM, under our Registration Statement on Form S-3 (File No. 333-260689) filed with the SEC on November 2, 2021. Sales of common stock, if any, pursuant to the Sales Agreement, may be made in sales deemed to be an “at the market offering” as defined in Rule 415(a) of the Securities Act, including sales made directly through The Nasdaq Global Market or on any other existing trading market for our common stock. During the year ended December 31, 2021, the Company did not sell any shares of common stock under the Sales Agreement. As of December 31, 2021, there was $100.0 million of common stock remaining available for sale under the ATM.

In December 2021, the Company entered into an exclusive License Agreement and a Share Purchase Agreement (the “Agreement”) for the development and commercialization of IMCIVREE (Setmelanotide) in China with RareStone Group Ltd. and received cash proceeds of $7,000.

At December 31, 2021, the Company had $294,855 of cash and cash equivalents and short-term investments on hand. In the future, the Company will be dependent on obtaining funding from third parties, such as proceeds from the issuance of debt, sale of equity, proceeds from out license arrangements, product sales 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”).

Dividend Policy

We have never paid a cash dividend on shares of our stock. We currently do not anticipate paying any cash dividends on our stock in the foreseeable future.

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.

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 currently operates in one business segment, which is the development and commercialization of therapies for patients with rare diseases. A single management team that reports to the Chief Executive Officer comprehensively manages the entire business. The Company does not operate separate lines of business with respect to its product or product candidates. Accordingly, the Company has one reportable segment.

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.

The Company is exposed to risks associated with extending credit to customers related to the sale of products. The Company does not require collateral to secure amounts due from its customers. At December 31, 2021, all of the Company’s revenue was generated from a single customer in the United States.

The Company relies on third-party manufacturers and suppliers for manufacturing and supply of its product. The inability of the suppliers or manufacturers to fulfill supply requirements of the Company could materially impact future operating results. A change in the relationship with the suppliers or manufacturer, or an adverse change in their business, could materially impact future operating results.

Cash and Cash Equivalents

The Company considers all highly liquid investments with 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 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, 2021, 2020, and 2019, the Company did not recognize any credit losses related to its available-for-sale debt securities. Further, as of December 31, 2021 and 2020, 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 card.

Accounts Receivable, net

Accounts receivable consists of amounts due from customers, net of customer allowances for cash discounts and any estimated expected credit losses. The Company's measurement of expected credit losses is based on relevant information about past events, including historical experience, current conditions, and reasonable and supportable forecasts that affect the collectability of the reported amount. To date, the Company has not experienced any credit losses. The Company's contract with its customer has standard payment terms that generally require payment within 45 days. The Company analyzes amounts that are past due for collectability, and periodically evaluates the creditworthiness of its customer. At December 31, 2021, the Company determined an allowance for doubtful account was not required based upon our review of contractual payments and our customer circumstances.

Revenue Recognition

The Company recognizes revenue in accordance with ASC Topic 606, *Revenue from Contracts with Customers*, or ASC 606. Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services in an amount that reflects the consideration which the entity expects to receive in exchange for those goods or services.

Product Revenue, Net

Subsequent to its regulatory approval in the U.S. on November 25, 2020, the Company began to sell IMCIVREE in the U.S. in March, 2021. The product is distributed through an exclusive third-party logistics, or 3PL, distribution agent that does not take title to the product. Once the product is delivered to the Company's exclusive specialty pharmacy provider, our sole customer in the U.S., the customer (or "wholesaler") takes title to the product. The wholesaler then distributes the product to health care providers and patients. In our exclusive distribution agreement with the 3PL

company, the Company acts as principal because we retain control of the product. The Company generally does not offer returns of product sold to the customer.

Revenue from product sales are recognized when the customer obtains control of our product, which occurs at a point in time, upon transfer of title to the customer because at that point in time we have no ongoing obligations to the customer. There are no other performance obligations besides the sale of product. We classify payments to our customer or other parties in the distribution channel for services that are distinct and priced at fair value as selling, general and administrative expenses in our consolidated statements of operations. Otherwise, payments to a customer or other parties in the distribution channel that do not meet those criteria are classified as a reduction of revenue, as discussed further below. Taxes collected from the customer relating to product sales and remitted to governmental authorities are excluded from revenue. Because our payment terms are generally forty-five days, the Company conclude there is not a significant financing component because the period between the transfer of a promised good or service to the customer and when the customer pays for that good or service will be one year or less. The Company expenses incremental costs of obtaining a contract as and when incurred since the expected amortization period of the asset that we would have recognized is one year or less.

Reserves for Variable Consideration

Revenues from product sales are recorded at the net sales price, or the transaction price, which includes estimates of variable consideration for which reserves are established and which result from discounts, returns, chargebacks, rebates, co-pay assistance and other allowances that are offered within contracts between us and our customer, health care providers and other indirect customers relating to the sale of IMCIVREE. These reserves are based on the amounts earned or to be claimed on the related sales and are classified as reductions of accounts receivable (if the amount is payable to the customer) or a current liability (if the amount is payable to a party other than a customer). Where appropriate, these estimates take into consideration a range of possible outcomes that are probability-weighted for relevant factors such as our historical experience, current contractual and statutory requirements, specific known market events and trends, industry data and forecasted customer buying and payment patterns. Overall, these reserves reflect our best estimates of the amount of consideration to which we are entitled based on the terms of the contract. The amount of variable consideration that is included in the transaction price may be constrained and is included in the net sales price only to the extent that it is considered probable that a significant reversal in the amount of the cumulative revenue recognized will not occur in a future period. Actual amounts of consideration ultimately received may differ from our estimates. If actual results in the future vary from our estimates, we will adjust these estimates, which would affect net product revenue and earnings in the period such variances become known.

The following are the components of variable consideration related to product revenue:

Chargebacks: The Company estimates obligations resulting from contractual commitments with the government and other entities to sell products to qualified healthcare providers and patients at prices lower than the list prices charged to our customer. The government and other entities charge us for the difference between what they pay for the product and the selling price to our customer. The Company records reserves for these chargebacks related to product sold to our customer during the reporting period, as well as our estimate of product that remains in the distribution channel at the end of the reporting period that we expect will be sold to qualified healthcare providers and patients in future periods.

Government rebates: The Company is subject to discount obligations under government programs, including Medicaid programs, Medicare and Tricare in the United States. We estimate Medicaid, Medicare and Tricare rebates based upon a range of possible outcomes that are probability-weighted for the estimated payer mix. These reserves are recorded in the same period the related revenue is recognized, resulting in a reduction of product revenue and the establishment of a liability that is included in accrued expenses on our consolidated balance sheet. For Medicare, we also estimate the number of patients in the prescription drug coverage gap for whom we will owe an additional liability under the Medicare Part D program. On a quarterly basis, we update our estimates and record any adjustments in the period that we identify the adjustments.

Trade discounts and allowances: The Company provides customary invoice discounts on IMCIVREE sales to our U.S. customer for prompt payment that are recorded as a reduction of revenue in the period the related product revenue

is recognized. In addition, we receive and pay for various distribution services from our customer in the distribution channel. For services that are either not distinct from the sale of our product or for which we cannot reasonably estimate the fair value, such fees are classified as a reduction of product revenue.

Product Returns: Our customer has limited return rights related to the product's damage or defect. The Company estimates the amount of product sales that may be returned and records the estimate as a reduction of revenue and a refund liability in the period the related product revenue is recognized. Based on the distribution model for IMCIVREE and the price of IMCIVREE, the Company believes there will be minimal returns.

Other incentives: Other incentives include co-payment assistance the Company provides to patients with commercial insurance that have coverage and reside in states that allow co-payment assistance. The calculation of the accrual for co-pay assistance is based on an estimate of claims and the cost per claim that we expect to receive associated with product that has been recognized as revenue. The estimate is recorded as a reduction of revenue in the same period the related revenue is recognized.

For the year ended December 31, 2021, we recorded product revenue, net, of $3,154. The table that summarizes balances and activity in each of the product revenue allowance and reserve categories has not been included due to the immateriality of the revenue recognized during the period.

Cost of Product Sales

Prior to receiving approval from the FDA in November 2020 to sell IMCIVREE in the United States, the Company expensed all costs incurred related to the manufacture of IMCIVREE as research and development expense because of the inherent risks associated with the development of a drug candidate, the uncertainty about the regulatory approval process and the lack of history for the Company of regulatory approval of drug candidates. Subsequent to receiving FDA approval in November 2020, the Company has capitalized a nominal amount of inventory related costs that were incurred subsequent to FDA approval. At December 31, 2021, the Company had $111 of inventory recorded as a component of other current assets on the consolidated balance sheet.

Intangible Assets, net

Definite-lived intangible assets related to capitalized milestones under license agreements are amortized on a straight-line basis over their remaining useful lives, which are estimated to be the remaining patent life. If our estimate of the product's useful life is shorter than the remaining patent life, then a shorter period is used. Amortization expense is recorded as a component of cost of sales on the consolidated statements of operations and comprehensive loss.

Impairment of Long-Lived Assets

The Company evaluates its long-lived assets, which consist primarily of property and equipment and finite lived intangible assets, for impairment whenever events or changes in circumstances indicate that the carrying amount of such assets may not be recoverable. Factors that the Company considers in deciding when to perform an impairment review include significant underperformance of the business in relation to expectations, significant negative industry or economic trends and significant changes or planned changes in the use of the assets. The Company measures recoverability of assets to be held and used by a comparison of the carrying amount of an asset to the future undiscounted net cash flows expected to be generated by the asset. If such assets are considered to be impaired, the Company measures the impairment to be recognized by the amount by which the carrying amount of the asset exceeds the fair value of the asset, less the cost to sell. No events or changes in circumstances existed to require an impairment assessment during the years ended December 31, 2021, 2020 and 2019.

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,	
	2021	2020
Prepaid research and development costs	$ 8,404	$ 5,828
Other current assets	4,103	3,048
Prepaid expenses and other current assets	$ 12,507	$ 8,876

Property and Equipment

Property and equipment consists of the following:

	Useful Life	December 31,	
		2021	2020
Leasehold improvements	*	$ 2,705	$ 2,705
Office equipment	5 years	107	70
Computers and software	3 years	1,010	625
Furniture, fixtures and equipment	5 years	1,249	1,237
		5,071	4,637
Less accumulated depreciation and amortization		(2,258)	(1,442)
Property and equipment, net		$ 2,813	$ 3,195

* Shorter of asset life or lease term.

Depreciation and amortization expense related to property and equipment for the years ended December 31, 2021, 2020 and 2019 was $816, $690, and $834, 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, 2021 and 2020 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, 2021 and 2020, respectively.

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 statements of operations. As of December 31, 2021 and 2020, no accrued interest or penalties are included on the related tax liability line in the consolidated balance sheets.

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, restricted stock units and performance 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,		
	2021	2020	2019
Stock options	5,737,599	5,199,235	3,428,497
Restricted stock units	435,589	176,537	—
Performance stock units	956,145	—	—
Potential common shares	7,129,333	5,375,772	3,428,497

Comprehensive Loss

Comprehensive 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 $332, $524 and $472 for the years ended December 31, 2021, 2020 and 2019, 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. See Note 14.

Application of New or Revised Accounting Standards

From time to time, new accounting pronouncements are issued by the FASB and adopted by the Company as of the specified effective date. Unless otherwise discussed, the Company believes that the impact of recently issued standards that are not yet effective will not have a material impact on its financial position or results of operations upon adoption.

In 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, 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. We have adopted ASU 2019-12 as of January 1, 2021 and the adoption of this standard did not have a material impact on the Company's financial position, results of operations and cash flows.

3. Accrued Expenses

Accrued expenses consists of the following:

	December 31, 2021	December 31, 2020
Research and development costs	$ 17,480	$ 5,815
Professional fees	2,163	648
Payroll related	8,371	5,916
Other	2,070	180
Accrued expenses	$ 30,084	$ 12,559

4. Fair Value of Financial Assets

As of December 31, 2021 and 2020, the carrying amount of cash and cash equivalents and short-term investments was $294,855 and $172,792, 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, 2021 using:			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash Equivalents:				
Commercial Paper	$ —	$ —	$ —	$ —
Money Market Funds	48,297	—	—	48,297
Marketable Securities:				
Corporate Debt Securities and Commercial Paper	—	235,607	—	235,607
Total	$ 48,297	$ 235,607	$ —	$ 283,904

	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
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

Marketable Securities

The following tables summarize the Company's marketable securities:

	December 31, 2021			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Assets				
Corporate debt securities and commercial paper (due within 1 year)	$ 235,608	$ 50	$ (51)	$ 235,607
	$ 235,608	$ 50	$ (51)	$ 235,607

	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

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 3.6 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, 2021, the Company has not entered into any lease arrangements classified as a finance lease.

Under FASB ASC Topic 842, *Leases*, 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, 2021, 2020 and 2019 were $551, $551 and $629, respectively.

Supplemental cash flow information related to the Company's lease for the years ended December 31, 2021 and 2020, includes cash payments of $802 and $786, respectively 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, 2021, all of which is under a non-cancellable operating lease:

	Operating Lease
2022	$ 818
2023	834
2024	851
2025	502
Thereafter	—
Total operating lease payments	3,005
Less: imputed interest	454
Total operating lease liability	$ 2,551

6. Intangible Assets, Net

As of December 31, 2021, the Company's definite-lived intangible assets, which totaled $4,658, resulted from the capitalization of certain milestone payments made to Ipsen Pharma, S.A.S., or Ipsen, in accordance with the terms of the Company's license agreement with Ipsen, in connection with the Company's first commercial sale of IMCIVREE in the U.S. in March 2021.

As of December 31, 2021, amortization expense for the next five years and beyond is summarized as follows:

2022	$ 455
2023	455
2024	455
2025	455
2026	455
Thereafter	2,383
Total	$ 4,658

The Company began amortizing its finite-lived intangible assets in April 2021 over an 11 year period based on IMCIVREE's expected patent exclusivity period. Amortization expense totaled $342 for the year ended December 31, 2021. Amortization expense is recorded as a component of cost of sales on the consolidated statements of operations and comprehensive loss.

7. Common Stock

Common Stock

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.

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.

8. Stock-based Compensation

2017 Equity Incentive Plan

The Rhythm Pharmaceuticals, Inc. 2017 Equity Incentive Plan (the "2017 Pan") 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, 2022, 2021 and 2020, 2,011,343, 1,769,436 and 1,759,870 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, 2021, an aggregate of 8,994,352 shares of common stock were authorized for issuance under the 2017 Plan, of which a total of approximately 1,865,019 shares of common stock remained available for future awards. In addition, a total of 7,129,333 shares of common stock reserved for issuance were subject to currently outstanding stock options, performance share units 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, 2021, 2020 and 2019, the Company granted 1,678,230, 2,546,075 and 1,445,200 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, 2021, 2020 and 2019 was $15.69, $13.25 and $17.19, respectively. The total intrinsic value of stock options exercised during the years ended December 31, 2021, 2020 and 2019 was $2,688, $2,661 and $3,844, 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,		
	2021	2020	2019
Risk-free interest rate	0.79 %	0.76 %	2.40 %
Expected term (in years)	6.11	6.08	6.07
Expected volatility	69.80 %	70.67 %	66.03 %
Expected dividend yield	—	—	—

A summary of the Company's stock option activity for the year ended December 31, 2021 is as follows:

	Number of Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term	Aggregate Intrinsic Value
Outstanding as of December 31, 2020	5,199,235	$ 21.30	7.57	$ 45,233
Granted	1,678,230	25.24	—	—
Exercised	(232,037)	17.81	—	2,688
Cancelled	(907,829)	26.04	—	—
Outstanding as of December 31, 2021	5,737,599	$ 21.84	6.73	$ 3,214
Options exercisable at December 31, 2021	2,861,174	$ 20.24	5.09	$ 3,178

The Company may grant Restricted Stock Units (RSUs) to employees and nonemployee directors. Each RSU represents a right to receive one share of the Company's common stock upon the completion of a specific period of continued service. RSU awards granted are valued at the market price of the Company's common stock on the date of grant. The Company recognizes stock-based compensation expense for the fair values of these RSUs on a straight-line basis over the requisite service period of these awards.

A summary of the Company's restricted stock unit activity for the year ended December 31, 2021 is as follows:

	Number of RSUs	Weighted-Average Grant Date Fair Value
Unvested as of December 31, 2020	176,537	$ 19.50
Granted	403,465	21.97
Vested	(27,583)	17.87
Cancelled	(116,830)	24.67
Unvested as of December 31, 2021	435,589	$ 15.74

As of December 31, 2021, the aggregate intrinsic value of non-vested RSUs was $4,347.

In November 2021, the Company granted up to a maximum of 956,145 Performance Stock Units (PSUs) to employees. Each PSU represents a right to receive one share of the Company's common stock upon vesting. The performance-based stock units granted in 2021 will vest on December 31, 2023 based upon i) continued service and ii) the achievement of specific clinical development and regulatory performance events, as approved by the compensation committee. PSU awards granted are valued at the market price of the Company's common stock on the date of grant. The Company recognizes stock-based compensation expense for the fair value of these PSUs for the awards that are probable of vesting over the service period. During each financial period, management estimates the probable number of PSU's that would vest until the ultimate achievement of the performance goal is known. At December 31, 2021, the Company estimates that 51.6% of the PSUs granted in November 2021 will be eligible to vest.

A summary of the Company's performance stock unit activity for the year ended December 31, 2021 is as follows:

	Number of PSUs	Weighted-Average Grant Date Fair Value
Unvested as of December 31, 2020	—	$ —
Granted	956,145	13.24
Vested	—	—
Cancelled	—	—
Unvested as of December 31, 2021	956,145	$ 13.24

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,		
	2021	2020	2019
Research and development	$ 7,687	$ 6,055	$ 5,163
Selling, general, and administrative	13,117	11,400	6,712
Total	$ 20,804	$ 17,455	$ 11,875

Stock-based compensation expense by award type recognized during the years ended December 31, 2021, 2020 and 2019 was as follows:

	Year Ended December 31,		
	2021	2020	2019
Stock options	$ 17,988	$ 15,915	$ 11,667
Employees stock purchase plan	310	180	208
Restricted stock units	1,924	1,360	—
Performance stock units	582	—	—
Total	$ 20,804	$ 17,455	$ 11,875

During 2021, 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 $141, $2,880 and $56, respectively.

As of December 31, 2021, the Company has unrecognized compensation cost of $35,694 related to non-vested employee, non-employee and director stock option awards that is expected to be recognized over a weighted-average period of 2.57 years. The Company has unrecognized compensation cost of $14,838 related to non-vested employee restricted stock unit and performance stock unit awards that is expected to be recognized over a weighted-average period of 2.30 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, 2021, a total of 962,942 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, 2021, 2020 and 2019, zero, 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, 2021, 38,051 shares were issued under this plan.

The purchase price of common stock under our ESPP is equal to 85.0% of the lower of (i) the market value per share of the common stock on the first business day of an offering period or (ii) the market value per share of the common stock on the purchase date. The fair value of the discounted purchases made under our ESPP is calculated using the Black-Scholes model. The fair value of the look-back provision plus the 15.0% discount is recognized as compensation expense over the 6 month purchase period.

9. Significant Agreements

License Agreements

RareStone Group Ltd.

In December 2021, the Company entered into an Exclusive License Agreement with RareStone Group Ltd., or the RareStone License. Pursuant to the RareStone License, we granted to RareStone an exclusive, sublicensable, royalty-bearing license under certain patent rights and know-how to develop, manufacture, commercialize and otherwise exploit any pharmaceutical product that contains setmelanotide in the diagnosis, treatment or prevention of conditions and diseases in humans in China, including mainland China, Hong Kong and Macao. RareStone has a right of first negotiation in the event that the Company chooses to grant a license to develop or commercialize the licensed product in Taiwan. The arrangement includes a license and an additional performance obligation to supply product upon the request of RareStone.

According to the terms of the RareStone License, RareStone has agreed to seek local approvals to commercialize IMCIVREE for the treatment of obesity and hyperphagia due to biallelic proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency, as well as Bardet-Biedl and Alström syndromes. Additionally, RareStone has agreed to fund efforts to identify and enroll patients from China in the Company's global EMANATE trial, a Phase 3, randomized, double-blind, placebo-controlled trial to evaluate setmelanotide in five independent sub-studies in patients with obesity due to a heterozygous variant of POMC/PCSK1 or LEPR; certain variants of the SRC1 gene, certain variants of the SH2B1 gene, or PCSK1 N221D deletions within the MC4R pathway. According to the terms of the RareStone License, RareStone made an upfront payment to Rhythm of $7,000 and issued $5,000 in equity to the Company. Rhythm will be eligible to receive development and commercialization milestones of up to $62,500, as well as tiered royalty payments on annual net sales of IMCIVREE. As of December 31, 2021, the Company received the upfront payment of $7,000, however the Company has not fulfilled its obligations related to the transfer of know how related to the license, and as such, the upfront payment was recorded as a contract liability on the consolidated balance sheet as of December 31, 2021. The $5,000 of RareStone equity was issued to Rhythm subsequent to December 31, 2021.

Ipsen Pharma S.A.S.

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 capitalized a $5,000 commercial milestone as a finite-lived intangible asset, as a result of the first commercial sale of IMCIVREE in the U.S. during March 2021. The Company recorded milestone expenses related to this license agreement of $3,000 during the year ended December 31, 2020. The expenses were recorded as research and development expenses when the milestone criteria were met in full during 2020. There are no research and development expenses related to milestones recorded in 2021 or 2019.

Camurus

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.

Takeda

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.*

10. Commitments and Contingencies

Legal Proceedings

The Company, from time to time, may be party to various litigation arising in the ordinary course of business. The Company is not presently subject to any pending or threatened litigation that it believes, if determined adversely to the Company, individually, or taken together, would reasonably be expected to have a material adverse effect on its business or financial results.

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 9 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, 2021, 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 $5,000 in commercial and development milestones, in connection with our license agreements. These milestones generally become due and payable upon achievement of such milestones or sales and achievement of development milestones. When the achievement of these milestones or sales have not occurred, such contingencies are not recorded in the Company's consolidated financial statements.

11. Related-Party Transactions

Amounts paid directly to consultants and vendors considered to be related parties amounted to $1,961, $3,221, and $2,489 for the years ended December 31, 2021, 2020 and 2019, respectively. Outstanding payments due to these related parties as of December 31, 2021 and 2020 were $50 and $187, respectively, and were included within accounts payable on the consolidated balance sheets.

12. Income Tax

For the years ended December 31, 2021, 2020 and 2019 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,		
	2021	2020	2019
Statutory tax rate	21.00 %	21.00 %	21.00 %
State tax, net of federal benefit	7.45 %	6.32 %	6.75 %
Research and development credit	2.94 %	1.46 %	2.49 %
Orphan drug credit	7.58 %	2.40 %	1.85 %
Tax law change	— %	— %	— %
Stock compensation	(1.05)%	(0.53)%	(0.10)%
Investor instrument revaluation	— %	— %	— %
Other	(0.47)%	(0.30)%	0.20 %
Change in valuation allowance	(37.45)%	(30.35)%	(32.19)%
Effective tax rate	— %	— %	— %

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

	As of December 31,	
	2021	2020
Deferred tax assets:		
Net operating loss carryforwards	$ 113,098	$ 102,367
Research and development credits	13,477	10,347
Orphan drug credit	15,385	10,110
Capitalized license fee	2,651	2,492
Stock-based compensation	9,150	6,621
Deferred revenue	1,901	—
Other	2,976	2,267
Total deferred tax assets	158,638	134,204
Valuation allowance	(158,211)	(133,596)
Net deferred tax assets	427	608
Deferred tax liabilities:		
Operating lease right-of-use asset and other	(427)	(608)
Total deferred tax liabilities	$ (427)	$ (608)

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, 2021 and 2020, 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 $24,615 in 2021 and $40,653 in 2020 primarily relates to the net loss incurred by the Company during each period.

As of December 31, 2021, the Company had federal and state net operating loss carryforwards of approximately $422,328 and $385,092, 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, 2021, $349,162 can be carried forward indefinitely.

As of December 31, 2021, the Company had federal and state research tax credits of approximately $10,161 and $4,197, respectively, which may be used to offset future tax liabilities. Additionally, as of 2021, the Company had a federal orphan drug credit related to qualifying research of $15,385. 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, 2021 and 2020. 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, 2021 and 2020, 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.

13. Retirement Plan

The Company has a 401(k) defined contribution plan for the benefit for all US employees and permits voluntary contributions by employees subject to IRS-imposed limitations. Beginning in 2021, the Company matched 100% of eligible employee contributions on the first 4% of employee salary (up to the IRS maximum). Contributions for the years ended December 31, 2021, 2020 and 2019 were $886, $321 and $0, respectively.

14. 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.

2022 Employment Inducement Plan

On February 9, 2022, the Company's board of directors adopted the Rhythm Pharmaceuticals, Inc. 2022 Employment Inducement Plan (the "Inducement Plan") without stockholder approval pursuant to Rule 5635(c)(4) of the Nasdaq Stock Market LLC listing rules ("Rule 5635(c)(4)"). In accordance with Rule 5635(c)(4), awards under the Inducement Plan may only be made to a newly hired employee who has not previously been a member of the Company's board of directors, or an employee who is being rehired following a bona fide period of non-employment by the Company or a subsidiary, as a material inducement to the employee's entering into employment with the Company or its subsidiary. An aggregate of 1,000,000 shares of the Company's common stock have been reserved for issuance under the Inducement Plan. The Company will continue to grant awards under the 2017 Plan pursuant to the terms thereof.

The exercise price of stock options granted under the Inducement Plan will not be less than the fair market value of a share of the Company's common stock on the grant date. Other terms of awards, including vesting requirements, are determined by the Company's board of directors and are subject to the provisions of the Inducement Plan. Stock options granted to employees generally vest over a four-year period but may be granted with different vesting terms. Certain options may provide for accelerated vesting in the event of a change in control. Stock options granted under the Inducement Plan expire no more than 10 years from the date of grant. As of March 1, 2022, no stock option awards have been issued under the Inducement Plan. As of March 1, 2022, no restricted stock unit awards have been granted under the Inducement Plan. As of March 1, 2022, 1,000,000 shares of common stock are available for future grant under the Inducement Plan

RHYTHM PHARMACEUTICALS, INC.

2022 EMPLOYMENT INDUCEMENT PLAN

Table Of Contents

RHYTHM PHARMACEUTICALS, INC.

2022 EMPLOYMENT INDUCEMENT PLAN

1. Purpose

This Plan is intended to provide incentives that will attract, retain and motivate highly competent officers, directors, employees, consultants and advisors to promote the success of the Company's business and align employees' interests with stockholders' interests.

2. Definitions

As used in this Plan, the following terms shall have the respective meanings set out below, unless the context clearly requires otherwise:

2.1. Accelerate, Accelerated, and Acceleration, means: (a) when used with respect to an Option or Stock Appreciation Right, that as of the time of reference such Option or Stock Appreciation Right will become exercisable with respect to some or all of the shares of Stock for which it was not then otherwise exercisable by its terms; (b) when used with respect to Restricted Stock or Restricted Stock Units, that the Risk of Forfeiture otherwise applicable to such Restricted Stock or Restricted Stock Units shall expire with respect to some or all of such shares of Restricted Stock or such Restricted Stock Units then still otherwise subject to the Risk of Forfeiture; and (c) when used with respect to Performance Units, that the applicable Performance Goals or other business objectives shall be deemed to have been met as to some or all of such Performance Units.

2.2. Affiliate means any parent or subsidiary corporation of the Company (within the meaning of Sections 424(e) and 424(f) of the Code, respectively).

2.3. Award means any grant or sale pursuant to the Plan of Options, Stock Appreciation Rights, Performance Units, Restricted Stock, Restricted Stock Units or Stock Grants.

2.4. Award Agreement means an agreement between the Company and the recipient of an Award, or other notice of grant of an Award, setting forth the terms and conditions of the Award.

2.5. Board means the Company's Board of Directors.

2.6. Change of Control means the occurrence of any of the following after the date of the approval of the Plan by the Board:

(a) a Transaction (as defined in Section 8.4), unless securities possessing more than 50% of the total combined voting power of the survivor's or acquiror's outstanding securities (or the securities of any parent thereof) are held by a person or persons who held securities possessing more than 50% of the total combined voting power of the Company's outstanding securities immediately prior to that Transaction; or

(b) any person or group of persons (within the meaning of Section 13(d)(3) of the Securities Exchange Act of 1934, as amended and in effect from time to time) that, directly or indirectly, acquires, including but not limited to by means of a merger or consolidation, beneficial ownership (determined pursuant to Securities and Exchange Commission Rule 13d-3 promulgated under the said Exchange Act) of securities possessing more than 50% of the total combined voting power of the Company's outstanding securities unless pursuant to a tender or exchange offer made directly to the

Company's stockholders that the Board recommends such stockholders accept, other than (i) the Company or any of its Affiliates, (ii) an employee benefit plan of the Company or any of its Affiliates, (iii) a trustee or other fiduciary holding securities under an employee benefit plan of the Company or any of its Affiliates, or (iv) an underwriter temporarily holding securities pursuant to an offering of such securities; or

(c) over a period of thirty-six (36) consecutive months or less, there is a change in the composition of the Board such that a majority of the Board members (rounded up to the next whole number, if a fraction) ceases, by reason of one or more proxy contests for the election of Board members, to be composed of individuals who either (i) have been Board members continuously since the beginning of that period, or (ii) have been elected or nominated for election as Board members during such period by at least a majority of the Board members described in the preceding clause (i) who were still in office at the time that election or nomination was approved by the Board; or

(d) a majority of the Board votes in favor of a decision that a Change of Control has occurred, which vote may adopted by the Board with the intention that such vote become effective subject to and contingent upon the occurrence of certain events, in which case such Change of Control shall not be deemed to have occurred unless and until such vote becomes effective in accordance with its terms.

2.7. Code means the Internal Revenue Code of 1986, as amended from time to time, or any successor statute thereto, and any regulations issued from time to time thereunder.

2.8. Committee means the Compensation Committee of the Board, which in general is responsible for the administration of the Plan, as provided in Section 5 of this Plan. For any period during which no such committee is in existence "Committee" shall mean the Board and all authority and responsibility assigned to the Committee under the Plan shall be exercised, if at all, by the Board.

2.9. Company means Rhythm Pharmaceuticals, Inc., a corporation organized under the laws of the State of Delaware.

2.10. Eligible Individual means any individual (a) not previously an employee or director of the Company or a subsidiary of the Company hired as a new employee or (b) rehired as an employee following a bona fide period of interruption of employment, in either case, if such person is granted an Award as a material inducement to his or her entering into employment with the Company or any Affiliate (within the meaning of the NASDAQ Rule 5635(c)(4)).

2.11. "Forfeiture," "forfeit," and derivations thereof, when used in respect of Restricted Stock purchased by a Participant, includes the Company's repurchase of such Restricted Stock at less than its then Market Value as a means intended to effect a forfeiture of value.

2.12. Grant Date means the date as of which an Option is granted, as determined under Section 7.1(a).

2.13. Incentive Option means an Option which by its terms is to be treated as an "incentive stock option" within the meaning of Section 422 of the Code.

2.14. Independent Director means a director who qualifies as "independent" within the meaning of NASDAQ Rule 5635(c)(4), or any successor rule, as such rule may be amended from time to time.

2.15. Market Value means the value of a share of Stock on a particular date determined by such methods or procedures as may be established by the Committee. Unless otherwise determined by the Committee, the Market Value of Stock as of any date is the closing price for the Stock as reported on the

NASDAQ Stock Market (or on any other national securities exchange on which the Stock is then listed) for that date or, if no closing price is reported for that date, the closing price on the first following date for which a closing price is reported. For purposes of Awards effective as of the effective date of the Company's initial public offering, Market Value of Stock shall be the price at which the Company's Stock is offered to the public in its initial public offering.

2.16. NASDAQ Rule 5635(c)(4) means NASDAQ Rule 5635(c)(4), or any successor rule, and all guidance and other interpretative authority thereunder, as such rule, guidance and other authority may be amended from time to time.

2.17. Nonstatutory Option means any option to purchase shares of Stock that is not an Incentive Option.

2.18. Option means a Nonstatutory Option.

2.19. Optionee means a Participant to whom an Option shall have been granted under the Plan.

2.20. Participant means an Eligible Individual to whom an Award is granted under the Plan or, if applicable, such other person who holds an outstanding award.

2.21. Performance Criteria means the criteria that the Committee selects for purposes of establishing the Performance Goal or Performance Goals for a Participant for a Performance Period. The Performance Criteria used to establish Performance Goals may include but are not limited to: (i) net earnings (either before or after one or more of (A) interest, (B) taxes, (C) depreciation and (D) amortization), (ii) gross or net sales or revenue, (iii) net income (either before or after taxes), (iv) adjusted net income, (v) operating earnings or profit, (vi) cash flow (including, but not limited to, operating cash flow and free cash flow, (vii) return on assets, (viii) return on capital, (ix) return on stockholders' equity, (x) total stockholder return, (xi) return on sales, (xii) gross or net profit or operating margin, (xiii) costs, (xiv) expenses, (xv) working capital, (xvi) earnings per share, (xvii) adjusted earnings per share, (xviii) price per share, (xix) regulatory body approval for commercialization of a product, (xx) implementation, completion or attainment of objectives relating to research, development, regulatory, commercial, or strategic milestones or developments; (xxi) market share, (xxii) economic value, (xxiii) revenue, (xxiv) revenue growth and (xxv) operational and organizational metrics.

2.22. Performance Goals means, for a Performance Period, the written goal or goals established by the Committee for the Performance Period based upon one or more of the Performance Criteria. The Performance Goals may be expressed in terms of overall Company performance or the performance of a division, business unit, subsidiary, or an individual, either individually, alternatively or in any combination, applied to either the Company as a whole or to a business unit or Affiliate, either individually, alternatively or in any combination, and measured either quarterly, annually or cumulatively over a period of years, on an absolute basis or relative to a pre-established target, to previous years' results or to a designated comparison group, in each case as specified by the Committee.

2.23. Performance Period means one or more periods of time, which may be of varying and overlapping durations, selected by the Committee, over which the attainment of one or more Performance Goals or other business objectives will be measured for purposes of determining a Participant's right to, and the payment of, an Award.

2.24. Performance Unit means a right granted to a Participant under Section 7.5, to receive cash, Stock or other Awards, the payment of which is contingent on achieving Performance Goals or other business objectives established by the Committee.

2.25. Plan means this 2022 Employment Inducement Plan of the Company, as amended from time to time, and including any attachments or addenda hereto.

2.26. Restricted Stock means a grant or sale of shares of Stock to a Participant subject to a Risk of Forfeiture.

2.27. Restricted Stock Units means rights to receive shares of Stock, cash or other Awards at the close of a Restriction Period, subject to a Risk of Forfeiture.

2.28. Restriction Period means the period of time, established by the Committee in connection with an Award of Restricted Stock or Restricted Stock Units, during which the shares of Restricted Stock or Restricted Stock Units are subject to a Risk of Forfeiture described in the applicable Award Agreement.

2.29. Risk of Forfeiture means a limitation on the right of the Participant to retain Restricted Stock or Restricted Stock Units, including a right of the Company to reacquire shares of Restricted Stock at less than their then Market Value, arising because of the occurrence or non-occurrence of specified events or conditions.

2.30. Stock means common stock, par value $0.001 per share, of the Company, and such other securities as may be substituted for such common stock pursuant to Section 8.

2.31. Stock Appreciation Right means a right to receive any excess in the Market Value of shares of Stock (except as otherwise provided in Section 7.2(c)) over a specified exercise price.

2.32. Stock Grant means the grant of shares of Stock not subject to restrictions or other forfeiture conditions.

2.33. Stockholders' Agreement means any agreement by and among the holders of at least a majority of the outstanding voting securities of the Company and setting forth, among other provisions, restrictions upon the transfer of shares of Stock or on the exercise of rights appurtenant thereto (including but not limited to voting rights).

3. Term of the Plan

The Plan became effective on the date on which the Plan was approved by the Board (the "Effective Date").

4. Stock Subject to the Plan

4.1. Plan Share Limitations.

(a) Limitation. The maximum number of shares of Stock that may be issued pursuant to Awards granted under the Plan shall not exceed 1,000,000 shares of Stock.

(b) Application. For purposes of applying the foregoing limitation of Section 4.1(a), (i) if any Option or Stock Appreciation Right expires, terminates, or is cancelled for any reason without having been exercised in full, or if any other Award is forfeited, the shares of Stock not purchased by the holder or subject to Awards which are forfeited, as the case may be, shall again be available for Awards to be granted under the Plan, (ii) if any Option is exercised by delivering previously owned shares of Stock or the withholding of a portion of the otherwise issuable shares of Stock subject to the Option in payment of the exercise price therefor, only the net number of shares, that is, the number of shares of Stock issued

minus the number received by the Company in payment of the exercise price, shall be considered to have been issued pursuant to an Award granted under the Plan, and (iii) any shares of Stock either delivered to or withheld by the Company in satisfaction of tax withholding obligations of the Company or an Affiliate with respect to an Award shall again be available for Awards to be granted under the Plan. In addition, settlement of any Award shall not count against the foregoing limitations except to the extent settled in the form of Stock. Shares of Stock issued pursuant to the Plan may be either authorized but unissued shares or shares held by the Company in its treasury.

4.2. Adjustment of Limitations. The share limitation of Section 4.1(a) shall be subject to adjustment pursuant to Section 8 of the Plan.

5. Administration

The Plan shall be administered by the Committee; provided, however, that at any time and on any one or more occasions the Board may itself exercise any of the powers and responsibilities assigned the Committee under the Plan and when so acting shall have the benefit of all of the provisions of the Plan pertaining to the Committee's exercise of its authorities hereunder. Subject to the provisions of the Plan, the Committee shall have complete authority, in its discretion, to make or to select the manner of making all determinations with respect to each Award to be granted by the Company under the Plan including the Eligible Individual to receive the Award and the form of Award. In making such determinations, the Committee may take into account the nature of the services rendered by the respective Eligible Individuals, their present and potential contributions to the success of the Company and its Affiliates, and such other factors as the Committee in its discretion shall deem relevant. Subject to the provisions of the Plan, the Committee shall also have complete authority to interpret the Plan, to prescribe, amend and rescind rules and regulations relating to it, to determine the terms and provisions of the respective Award Agreements (which need not be identical), and to make all other determinations necessary or advisable for the administration of the Plan. The Committee may adopt procedures from time to time that are intended to ensure that an individual is an Eligible Individual prior to the granting of any Awards to such individual (including without limitation a requirement that each such individual certify to the Company prior to the receipt of an Award that he or she is not currently employed by the Company or any Affiliate and, if previously so employed, has had a bona fide period of interruption of employment, and that the grant of Awards is an inducement material to his or her agreement to enter into employment with the Company or its Affiliate). The Committee's determinations made in good faith on matters referred to in the Plan shall be final, binding and conclusive on all persons having or claiming any interest under the Plan or an Award made pursuant hereto.

6. Authorization of Grants

6.1. Eligibility. The Committee may grant from time to time and at any time prior to the termination of the Plan one or more Awards, either alone or in combination with any other Awards, to any Eligible Individual.

6.2. General Terms of Awards. Each grant of an Award shall be subject to all applicable terms and conditions of the Plan (including but not limited to any specific terms and conditions applicable to that type of Award set out in the following Section), and such other terms and conditions, not inconsistent with the terms of the Plan, as the Committee may prescribe. No prospective Participant shall have any rights with respect to an Award, unless and until such Participant shall have complied with the applicable terms and conditions of such Award (including if applicable delivering a fully executed copy of any agreement evidencing an Award to the Company).

6.3. Effect of Termination of Employment, Etc. Unless the Committee shall provide otherwise

with respect to any Award (including, but not limited to, in a Participant's Award Agreement), if the Participant's employment or other association with the Company and its Affiliates ends for any reason, including because of the Participant's employer ceasing to be an Affiliate, (a) any outstanding Option or Stock Appreciation Right of the Participant shall cease to be exercisable in any respect not later than ninety (90) days following that event and, for the period it remains exercisable following that event, shall be exercisable only to the extent exercisable at the date of that event, and (b) any other outstanding Award of the Participant to the extent that it is then still subject to Risk of Forfeiture shall be forfeited or otherwise subject to return to or repurchase by the Company on the terms specified in the applicable Award Agreement. Cessation of the performance of services in one capacity, for example, as an employee, shall not result in termination of an Award while the Participant continues to perform services in another capacity, for example as a director. Military or sick leave or other bona fide leave approved by the Company shall not be deemed a termination of employment or other association. To the extent consistent with applicable law, the Committee may provide that Awards continue to vest for some or all of the period of any such leave, or that their vesting shall be tolled during any such leave and only recommence upon the Participant's return from leave, if ever.

6.4. Non-Transferability of Awards. Except as otherwise provided in this Section 6.4, Awards shall not be transferable, and no Award or interest therein may be sold, transferred, pledged, assigned, or otherwise alienated or hypothecated, other than by will or by the laws of descent and distribution. The provisions of the immediately preceding sentence shall not be applicable to Stock Grants which shall not be subject to any transfer restrictions under this Section 6.4. All of a Participant's rights in any Award may be exercised during the life of the Participant only by the Participant or the Participant's legal representative. However, the Committee may, at or after the grant of an Award of an Option, or shares of Restricted Stock, provide that such Award may be transferred by the recipient to a family member; *provided, however*, that any such transfer is without payment of any consideration whatsoever and that no transfer shall be valid unless first approved by the Committee, acting in its sole discretion. For this purpose, "family member" means any child, stepchild, grandchild, parent, grandparent, stepparent, spouse, former spouse, sibling, niece, nephew, mother-in-law, father-in-law, son-in-law, daughter-in-law, brother-in-law, or sister-in-law, including adoptive relationships, any person sharing the employee's household (other than a tenant or employee), a trust in which the foregoing persons have more than fifty (50) percent of the beneficial interests, a foundation in which the foregoing persons (or the Participant) control the management of assets, and any other entity in which these persons (or the Participant) own more than fifty (50) percent of the voting interests.

7. Specific Terms of Awards

7.1. Options.

(a) Date of Grant. The granting of an Option shall take place at the time specified in the Award Agreement.

(b) Exercise Price. The price at which shares of Stock may be acquired under each Option shall be not less than 100% of the Market Value of Stock on the Grant Date.

(c) Option Period. No Option may be exercised on or after the tenth (10th) anniversary of the Grant Date.

(d) Exercisability. An Option may be immediately exercisable or become exercisable in such installments, cumulative or non-cumulative, as the Committee may determine. In the case of an Option not otherwise immediately exercisable in full, the Committee may Accelerate such Option in whole or in part at any time.

(e) Method of Exercise. An Option may be exercised by the Optionee giving written notice, in the manner provided in Section 18, specifying the number of shares of Stock with respect to which the Option is then being exercised. The notice shall be accompanied by payment in the form of cash or check payable to the order of the Company in an amount equal to the exercise price of the shares of Stock to be purchased or, subject in each instance to the Committee's approval, acting in its sole discretion, and to such conditions, if any, as the Committee may deem necessary to avoid adverse accounting effects to the Company,

(i) by delivery to the Company of shares of Stock having a Market Value equal to the exercise price of the shares to be purchased, or

(ii) by the Company withholding shares of Stock otherwise issuable under the Option with such withheld shares having an aggregate Market Value equal to the aggregate exercise price of the shares to be purchased, or

(iii) unless prohibited by applicable law, by delivery to the Company of the Optionee's executed promissory note in the principal amount equal to the exercise price of the shares of Stock to be purchased and otherwise in such form as the Committee shall have approved.

If the Stock is traded on an established market, payment of any exercise price may also be made through and under the terms and conditions of any formal cashless exercise program authorized by the Company entailing the sale of the Stock subject to an Option in a brokered transaction (other than to the Company). Receipt by the Company of such notice and payment in any authorized or combination of authorized means shall constitute the exercise of the Option. Within thirty (30) days thereafter but subject to the remaining provisions of the Plan, the Company shall deliver or cause to be delivered to the Optionee or his agent a certificate or certificates or shall cause the Stock to be held in book-entry position through the direct registration system of the Company's transfer agent for the number of shares then being purchased. Such shares of Stock shall be fully paid and nonassessable.

7.2. Stock Appreciation Rights.

(a) Tandem or Stand-Alone. Stock Appreciation Rights may be granted in tandem after the award of the Option, or alone and unrelated to an Option. Stock Appreciation Rights in tandem with an Option shall terminate to the extent that the related Option is exercised, and the related Option shall terminate to the extent that the tandem Stock Appreciation Rights are exercised.

(b) Exercise Price. Stock Appreciation Rights shall have an exercise price of not less than one hundred percent (100%) of the Market Value of the Stock on the date of award, or in the case of Stock Appreciation Rights in tandem with Options, the exercise price of the related Option.

(c) Other Terms. Except as the Committee may deem inappropriate or inapplicable in the circumstances, Stock Appreciation Rights shall be subject to terms and conditions substantially similar to those applicable to an Option. In addition, a Stock Appreciation Right related to an Option which can only be exercised during limited periods following a Change of Control may entitle the Participant to receive an amount based upon the highest price paid or offered for Stock in any transaction relating to the Change of Control or paid during the thirty (30) day period immediately preceding the occurrence of the Change of Control in any transaction reported in the stock market in which the Stock is normally traded.

7.3. Restricted Stock.

(a) Purchase Price. Shares of Restricted Stock shall be issued under the Plan for such consideration, if any, in cash, other property or services, or any combination thereof, as is determined by the Committee.

(b) Issuance of Stock. Each Participant receiving a Restricted Stock Award, subject to subsection (c) below, shall be issued a stock certificate in respect of such shares of Restricted Stock or the shares shall be held in book-entry position through the direct registration system of the Company's transfer agent. If a certificate is issued, such certificate shall be registered in the name of such Participant, and, if applicable, shall bear an appropriate legend referring to the terms, conditions, and restrictions applicable to such Award substantially in the following form:

> "The shares evidenced by this certificate are subject to the terms and conditions of Rhythm Pharmaceuticals, Inc.'s 2022 Employment Inducement Plan and an Award Agreement entered into by the registered owner and Rhythm Pharmaceuticals, Inc., copies of which will be furnished by the Company to the holder of the shares evidenced by this certificate upon written request and without charge."

If the Stock is in book-entry position through the direct registration system of the Company's transfer agent, the restrictions will be appropriately noted.

(c) Escrow of Shares. The Committee may require that any stock certificates evidencing shares of Restricted Stock be held in custody by a designated escrow agent (which may but need not be the Company) until the restrictions thereon shall have lapsed, and that the Participant deliver a stock power, endorsed in blank, relating to the Stock covered by such Award.

(d) Restrictions and Restriction Period. During the Restriction Period applicable to shares of Restricted Stock, such shares shall be subject to limitations on transferability and a Risk of Forfeiture arising on the basis of such conditions related to the performance of services, Company or Affiliate performance or otherwise as the Committee may determine and provide for in the applicable Award Agreement. Any such Risk of Forfeiture may be waived or terminated, or the Restriction Period shortened, at any time by the Committee on such basis as it deems appropriate.

(e) Rights Pending Lapse of Risk of Forfeiture or Forfeiture of Award. Except as otherwise provided in the Plan or the applicable Award Agreement, the Participant shall have all of the rights of a stockholder of the Company with respect to any outstanding shares of Restricted Stock, including the right to vote, and the right to receive any dividends with respect to, the shares of Restricted Stock (but any dividends or other distributions payable in shares of Stock or other securities of the Company shall constitute additional Restricted Stock, subject to the same Risk of Forfeiture as the shares of Restricted Stock in respect of which such shares of Stock or other securities are paid). The Committee, as determined at the time of Award, may permit or require the payment of cash dividends to be deferred and, if the Committee so determines, reinvested in additional Restricted Stock to the extent shares of Stock are available under Section 4.

(f) Lapse of Restrictions. If and when the Restriction Period expires without a prior forfeiture, any certificates for such shares shall be delivered to the Participant promptly if not theretofore so delivered.

7.4. Restricted Stock Units.

(a) Character. Subject to Section 10, each Restricted Stock Unit shall entitle the recipient to a share of Stock at a close of such Restriction Period as the Committee may establish and subject

to a Risk of Forfeiture arising on the basis of such conditions relating to the performance of services, Company or Affiliate performance or otherwise as the Committee may determine and provide for in the applicable Award Agreement. Any such Risk of Forfeiture may be waived or terminated, or the Restriction Period shortened, at any time by the Committee on such basis as it deems appropriate.

(b) Form and Timing of Payment. Payment of earned Restricted Stock Units shall be made promptly following the close of the applicable Restriction Period. At the discretion of the Committee, Participants may be entitled to receive payments equivalent to any dividends declared with respect to Stock referenced in grants of Restricted Stock Units but only following the close of the applicable Restriction Period and then only if the underlying Stock shall have been earned. Unless the Committee shall provide otherwise, any such dividend equivalents shall be paid, if at all, without interest or other earnings. The Committee may permit or, if it so provides at grant require, a Participant to defer such Participant's receipt of the payment that would otherwise be due to such Participant with respect to Restricted Stock Units. If any such deferral election is required or permitted, the Committee shall establish rules and procedures for such payment deferrals.

7.5. Performance Units.

(a) Character. Each Performance Unit shall entitle the recipient to the value of a specified number of shares of Stock, over the initial value for such number of shares, if any, established by the Committee at the time of grant, at the close of a specified Performance Period to the extent specified business objectives, including but not limited to Performance Goals, shall have been achieved.

(b) Earning of Performance Units. The Committee shall set Performance Goals or other business objectives in its discretion which, depending on the extent to which they are met within the applicable Performance Period, will determine the number and value of Performance Units that will be paid out to the Participant. After the applicable Performance Period has ended, the holder of Performance Units shall be entitled to receive payout on the number and value of Performance Units earned by the Participant over the Performance Period, to be determined as a function of the extent to which the corresponding Performance Goals or other business objectives have been achieved.

(c) Form and Timing of Payment. Unless otherwise provided in the applicable Award Agreement, payment of earned Performance Units shall be made in a single lump sum following the close of the applicable Performance Period. At the discretion of the Committee, Participants may be entitled to receive any dividends declared with respect to Stock which have been earned in connection with grants of Performance Units which have been earned, but not yet distributed to Participants. The Committee may permit or, if it so provides at grant require, a Participant to defer such Participant's receipt of the payment of cash or the delivery of Stock that would otherwise be due to such Participant by virtue of the satisfaction of any requirements or goals with respect to Performance Units. If any such deferral election is required or permitted, the Committee shall establish rules and procedures for such payment deferrals.

7.6. Stock Grants. Stock Grants shall be awarded solely in recognition of significant prior or expected contributions to the success of the Company or its Affiliates, as an inducement to employment, in lieu of compensation otherwise already due and in such other limited circumstances as the Committee deems appropriate. Stock Grants shall be made without forfeiture conditions of any kind.

7.7. Awards to Participants Outside the United States. The Committee may modify the terms of any Award under the Plan granted to a Participant who is, at the time of grant or during the term of the Award, resident or primarily employed outside of the United States in any manner deemed by the Committee to be necessary or appropriate in order that the Award shall conform to laws, regulations, procedures, and customs of the country in which the Participant is then resident or primarily employed, or

so that the value and other benefits of the Award to the Participant, as affected by foreign tax laws and other restrictions applicable as a result of the Participant's residence or employment abroad, shall be as comparable as practicable to the value of such an Award to a Participant who is resident or primarily employed in the United States. The Committee may establish supplements or sub-plans to, or amendments, restatements, or alternative versions of, the Plan for the purpose of granting and administrating any such modified Award. No such modification, supplement, sub-plan, amendment, restatement or alternative version may increase the share limit of Section 4.

8. Adjustment Provisions

8.1. Adjustment for Corporate Actions. All of the share numbers set forth in the Plan reflect the capital structure of the Company as of the Effective Date. If subsequent to that date the outstanding shares of Stock (or any other securities covered by the Plan by reason of the prior application of this Section) are increased, decreased, or exchanged for a different number or kind of shares or other securities, or if additional shares or new or different shares or other securities are distributed with respect to shares of Stock, as a result of a reorganization, recapitalization, reclassification, stock dividend, stock split, reverse stock split, or other similar distribution with respect to such shares of Stock, an equitable adjustment will be made in (i) the maximum numbers and kinds of shares provided in Section 4, (ii) the numbers and kinds of shares or other securities subject to the then outstanding Awards, (iii) the exercise price for each share or other unit of any other securities subject to then outstanding Options and Stock Appreciation Rights (without change in the aggregate purchase price as to which such Options or Rights remain exercisable), and (iv) the repurchase price of each share of Restricted Stock then subject to a Risk of Forfeiture in the form of a Company repurchase right.

8.2. Adjustment of Awards Upon the Occurrence of Certain Unusual or Nonrecurring Events. In the event of any corporate action not specifically covered by the preceding Section, including but not limited to an extraordinary cash distribution on Stock, a corporate separation or other reorganization or liquidation, the Committee shall make such adjustment of outstanding Awards and their terms, if any, as it, in its sole discretion, may deem equitable in the circumstances. The Committee may make adjustments in the terms and conditions of, and the criteria included in, Awards in recognition of unusual or nonrecurring events (including, without limitation, the events described in this Section) affecting the Company or the financial statements of the Company or of changes in applicable laws, regulations, or accounting principles, whenever the Committee determines that such adjustments are appropriate in order to prevent dilution or enlargement of the benefits or potential benefits intended to be made available under the Plan.

8.3. Related Matters. Any adjustment in Awards made pursuant to Section 8.1 or Section 8.2 shall be determined and made, if at all, by the Committee, acting in its sole discretion, and shall include any correlative modification of terms, including of Option exercise prices, rates of vesting or exercisability, Risks of Forfeiture, applicable repurchase prices for Restricted Stock, and Performance Goals and other business objectives which the Committee may deem necessary or appropriate so as to ensure the rights of the Participants in their respective Awards are not substantially diminished nor enlarged as a result of the adjustment and corporate action other than as expressly contemplated in this Section 8. The Committee, in its discretion, may determine that no fraction of a share of Stock shall be purchasable or deliverable upon exercise, and in that event if any adjustment hereunder of the number of shares of Stock covered by an Award would cause such number to include a fraction of a share of Stock, such number of shares of Stock shall be adjusted to the nearest smaller whole number of shares. No adjustment of an Option exercise price per share pursuant to Section 8.1 or Section 8.2 shall result in an exercise price which is less than the par value of the Stock.

8.4. Transactions.

(a) Definition of Transaction. In this Section 8.4, "Transaction" means (1) any merger or consolidation of the Company with or into another entity as a result of which the Stock of the Company is converted into or exchanged for the right to receive cash, securities or other property or is cancelled, (2) any sale or exchange of all or substantially all of the outstanding Stock of the Company for cash, securities or other property, (3) any sale, transfer, or other disposition of all or substantially all of the Company's assets to one or more other persons in a single transaction or series of related transactions or (4) any liquidation or dissolution of the Company.

(b) Treatment of Awards. In a Transaction, the Committee may take any one or more of the following actions as to all or any (or any portion of) outstanding Awards, subject to the provisions of Section 9 of this Plan.

(1) Provide that any Awards shall be assumed, or substantially equivalent rights shall be provided in substitution therefor, by the acquiring or succeeding entity (or an affiliate thereof).

(2) Upon written notice to the holders, provide that all or any of the holders' unexercised outstanding Options and Stock Appreciation Rights (collectively, "Rights") will terminate immediately prior to the consummation of such Transaction unless exercised within a specified period following the date of such notice.

(3) Provide that all or any Awards that are subject to Risk of Forfeiture will terminate immediately prior to the consummation of such Transaction.

(4) Provide that all or any outstanding Rights shall Accelerate so as to become exercisable prior to or upon such Transaction with respect to some or all of the shares of Stock for which any such Rights would not then otherwise be exercisable by their terms.

(5) Provide that all or any outstanding Awards that are subject to Risk of Forfeiture shall Accelerate so that the Risk of Forfeiture otherwise applicable to such Awards shall expire prior to or upon such Transaction with respect to any such Awards that would then still otherwise be subject to the Risk of Forfeiture.

(6) Provide for cash payments, net of applicable tax withholdings, to be made to holders equal to the excess, if any, of (A) the acquisition price times the number of shares of Stock subject to an Option and Stock Appreciation Right (in each case, to the extent the exercise price does not exceed the acquisition price) over (B) the aggregate exercise price for all such shares of Stock subject to the Option or Stock Appreciation Right as applicable, in exchange for the termination of such Option and Stock Appreciation Right; provided, that if the acquisition price does not exceed the exercise price of any such Option or Stock Appreciation Right, the Committee may cancel that Option and Stock Appreciation Right without the payment of any consideration therefore prior to or upon the Transaction. For purposes of this paragraph 6 and paragraph 7 below, "acquisition price" means the amount of cash, and market value of any other consideration, received in payment for a share of Stock surrendered in a Transaction but need not take into account any deferred consideration unless and until received.

(7) Provide for cash payments, net of applicable tax withholdings, to be made to holder or holders of all or any Awards (other than Options and Stock Appreciation Rights) equal to the acquisition price times the number of shares of Stock

subject to any such Awards, in exchange for the termination of any such Awards; provided, that the Committee may cancel, pursuant to paragraph 3 above, any such Award that is subject to a Risk of Forfeiture at the time of the consummation of such Transaction without the payment of any consideration therefor prior to or upon the Transaction.

(8) Provide that, in connection with a liquidation or dissolution of the Company, all or any Awards (other than Restricted Stock or Stock Grants) shall convert into the right to receive liquidation proceeds net of the exercise price thereof and any applicable tax withholdings.

(9) Any combination of the foregoing.

In the event that the Committee determines in its discretion to take the actions contemplated under paragraph (1) above of this Section 8.4(b) with respect to all or any Awards, the Committee shall ensure that, upon consummation of the Transaction, any such Awards are assumed and/or exchanged or replaced with another similar award issued by the acquiring or succeeding entity (or an affiliate thereof) and that, as a result of such assumption and/or exchange or replacement, the holder of such assumed Award and/or such exchanged or replaced similar award has the right to purchase or receive the value of, for each share of Stock subject to such Award immediately prior to the consummation of the Transaction, the consideration (whether cash, securities or other property) received as a result of the Transaction by holders of Stock for each share of Stock held immediately prior to the consummation of the Transaction (and if holders were offered a choice of consideration, the type of consideration chosen by the holders of a majority of the outstanding shares of Stock); *provided, however*, that if such consideration received as a result of the Transaction is not solely common stock (or its equivalent) of the acquiring or succeeding entity (or an affiliate thereof), the Committee may, with the consent of the acquiring or succeeding entity (or an affiliate thereof), provide for the consideration to be received with respect to such assumed Award and/or such exchanged or replaced similar award to consist of or be based solely on common stock (or its equivalent) of the acquiring or succeeding entity (or an affiliate thereof) equivalent in value to the per share consideration received by holders of outstanding shares of Stock as a result of the Transaction; and *provided*, *further*, that if such Award is an Option, the holder of such Option must exercise the Option and make payment of the applicable exercise price in connection therewith in order to receive such consideration.

(c) Treatment of Other Awards. Upon the occurrence of a Transaction other than a liquidation or dissolution of the Company which is not part of another form of Transaction, then, subject to the provisions of Section 9 below, with respect to all outstanding Awards (other than Options and Stock Appreciation Rights) that are not terminated prior to or upon such Transaction, the repurchase and other rights of the Company under each such Award shall inure to the benefit of the Company's successor and any forfeiture restrictions shall continue to apply and shall, unless the Committee determines otherwise, apply to the cash, securities or other property which the Stock was converted into or exchanged for pursuant to such Transaction in the same manner and to the same extent as they applied to the Award.

(d) Related Matters. In taking any of the actions permitted under this Section 8.4, the Committee shall not be obligated to treat all Awards, all Awards held by a Participant, or all Awards of the same type, identically. Any determinations required to carry out the foregoing provisions of this Section 8.4, including but not limited to the market value of other consideration received by holders of Stock in a Transaction and whether substantially equivalent Rights have been substituted, shall be made by the Committee acting in its sole discretion. In connection with any action or actions taken by the Committee in respect of Awards and in connection with a Transaction, the Committee may require such acknowledgements of satisfaction and releases from Participants as it may determine.

9. Change of Control

Except as otherwise provided below, upon the occurrence of a Change of Control, to the extent that the surviving entity declines to continue, convert, assume or replace outstanding Awards, then, notwithstanding anything express or implied to the contrary in Section 8.4 above:

(a) any and all Options and Stock Appreciation Rights not already exercisable in full shall Accelerate with respect to 100% of the shares for which such Options or Stock Appreciation Rights are not then exercisable;

(b) any Risk of Forfeiture applicable to Restricted Stock and Restricted Stock Units which is not based on achievement of Performance Goals or other business objectives shall lapse with respect to 100% of the Restricted Stock and Restricted Stock Units still subject to such Risk of Forfeiture immediately prior to the Change of Control; and

(c) all outstanding Awards of Restricted Stock and Restricted Stock Units conditioned on the achievement of Performance Goals or other business objectives and the payouts attainable under outstanding Performance Units shall be deemed to have been satisfied at target as of the effective date of the Change of Control, except if and to the extent otherwise determined by the Committee in its sole discretion at any time prior to, or upon, such Change of Control.

All such Awards of Performance Units and Restricted Stock Units shall be paid to the extent earned to Participants in accordance with their terms within thirty (30) days following the effective date of the Change of Control. None of the foregoing shall apply, however, (i) in the case of any Award pursuant to an Award Agreement requiring other or additional terms upon a Change of Control (or similar event), or (ii) if specifically prohibited under applicable laws, or by the rules and regulations of any governing governmental agencies or national securities exchanges.

10. Settlement of Awards

10.1. In General. Options and Restricted Stock shall be settled in accordance with their terms. All other Awards may be settled in cash, Stock, or other Awards, or a combination thereof, as determined by the Committee at or after grant and subject to any contrary Award Agreement. The Committee may not require settlement of any Award in Stock pursuant to the immediately preceding sentence to the extent issuance of such Stock would be prohibited or unreasonably delayed by reason of any other provision of the Plan.

10.2. Violation of Law. Notwithstanding any other provision of the Plan or the relevant Award Agreement, if, at any time, in the reasonable opinion of the Company, the issuance of shares of Stock covered by an Award may constitute a violation of law, then the Company may delay such issuance until (i) approval shall have been obtained from such governmental agencies, other than the Securities and Exchange Commission, as may be required under any applicable law, rule, or regulation and (ii) in the case where such issuance would constitute a violation of a law administered by or a regulation of the Securities and Exchange Commission, one of the following conditions shall have been satisfied:

(a) the shares of Stock are at the time of the issue of such shares effectively registered under the Securities Act of 1933, as amended; or

(b) the Company shall have determined, on such basis as it deems appropriate (including an opinion of counsel in form and substance satisfactory to the Company) that the sale, transfer, assignment, pledge, encumbrance or other disposition of such shares does not require registration under the

Securities Act of 1933, as amended or any applicable State securities laws.

Furthermore, the inability of the Company to obtain or maintain, or the impracticability of it obtaining or maintaining, authority from any governmental agency having jurisdiction, which authority is deemed by the Company's counsel to be necessary to the lawful issuance of any Stock hereunder, shall relieve the Company of any liability in respect of the failure to issue such Stock as to which such requisite authority shall not have been obtained, and shall constitute circumstances in which the Committee may determine to amend or cancel Awards pertaining to such Stock, with or without consideration to the affected Participants.

10.3. Corporate Restrictions on Rights in Stock. Any Stock to be issued pursuant to Awards granted under the Plan shall be subject to all restrictions upon the transfer thereof which may be now or hereafter imposed by the certificate of incorporation, and bylaws.

10.4. Investment Representations. The Company shall be under no obligation to issue any shares of Stock covered by any Award unless the shares to be issued pursuant to Awards granted under the Plan have been effectively registered under the Securities Act of 1933, as amended, or the Participant shall have made such written representations to the Company (upon which the Company believes it may reasonably rely) as the Company may deem necessary or appropriate for purposes of confirming that the issuance of such shares will be exempt from the registration requirements of that Act and any applicable state securities laws and otherwise in compliance with all applicable laws, rules and regulations of any jurisdiction in which Participants may reside or primarily work, including but not limited to that the Participant is acquiring the shares for his or her own account for the purpose of investment and not with a view to, or for sale in connection with, the distribution of any such shares.

10.5. Registration. If the Company shall deem it necessary or desirable to register under the Securities Act of 1933, as amended, or other applicable statutes any shares of Stock issued or to be issued pursuant to Awards granted under the Plan, or to qualify any such shares of Stock for exemption from the Securities Act of 1933, as amended or other applicable statutes, then the Company shall take such action at its own expense. The Company may require from each recipient of an Award, or each holder of shares of Stock acquired pursuant to the Plan, such information in writing for use in any registration statement, prospectus, preliminary prospectus or offering circular as is reasonably necessary for that purpose and may require reasonable indemnity to the Company and its officers and directors from that holder against all losses, claims, damage and liabilities arising from use of the information so furnished and caused by any untrue statement of any material fact therein or caused by the omission to state a material fact required to be stated therein or necessary to make the statements therein not misleading in the light of the circumstances under which they were made. In addition, the Company may require of any such person that he or she agree that, without the prior written consent of the Company or the managing underwriter in any public offering of shares of Stock, he or she will not sell, make any short sale of, loan, grant any option for the purchase of, pledge or otherwise encumber, or otherwise dispose of, any shares of Stock during the 180 day period commencing on the effective date of the registration statement relating to the underwritten public offering of securities (or during such shorter or longer period of time as the Committee shall determine in its sole discretion, which period of time shall commence from and after such effective date of such registration statement). Without limiting the generality of the foregoing provisions of this Section 10.5, if in connection with any underwritten public offering of securities of the Company the managing underwriter of such offering requires that the Company's directors and officers enter into a lock-up agreement containing provisions that are more restrictive than the provisions set forth in the preceding sentence, then (a) each holder of shares of Stock acquired pursuant to the Plan (regardless of whether such person has complied or complies with the provisions of clause (b) below) shall be bound by, and shall be deemed to have agreed to, the same lock-up terms as those to which the Company's directors and officers are required to adhere; and (b) at the request of the Company or such managing underwriter, each such person shall execute and deliver a lock-up agreement in form and substance equivalent to that which is required to be executed by

the Company's directors and officers.

10.6. Placement of Legends; Stop Orders; etc. Each share of Stock to be issued pursuant to Awards granted under the Plan may bear a reference to the investment representations made in accordance with Section 10.4 in addition to any other applicable restrictions under the Plan, and the terms of the Award and, if applicable, to the fact that no registration statement has been filed with the Securities and Exchange Commission in respect to such shares of Stock. All shares of Stock or other securities issued under the Plan shall be subject to such stop transfer orders and other restrictions as the Committee may deem advisable under the rules, regulations, and other requirements of any stock exchange upon which the Stock is then listed, and any applicable federal or state securities law, and the Committee may cause a legend or legends to be placed on any such certificates to make appropriate reference to such restrictions, or, if the Stock will be held in book-entry position through the direct registration system of the Company's transfer agent, the restrictions will be appropriately noted.

10.7. Tax Withholding. Whenever shares of Stock are issued or to be issued pursuant to Awards granted under the Plan, the Company shall have the right to require the recipient to remit to the Company an amount sufficient to satisfy federal, state, local, foreign or other withholding tax requirements if, when, and to the extent required by law (whether so required to secure for the Company an otherwise available tax deduction or otherwise) prior to the delivery of any certificate or certificates, held in book-entry position through the direct registration system of the Company's transfer agent, for such shares. The obligations of the Company under the Plan shall be conditional on satisfaction of all such withholding obligations and the Company shall, to the extent permitted by law, have the right to deduct any such taxes from any payment of any kind otherwise due to a Participant or to utilize any other withholding method prescribed by the Committee from time to time. However, in such cases Participants may elect, subject to the approval of the Committee, acting in its sole discretion, to satisfy an applicable withholding requirement, in whole or in part, by having the Company withhold shares of Stock to satisfy their tax obligations. All elections shall be irrevocable, made in writing, signed by the Participant, and shall be subject to any restrictions or limitations that the Committee deems appropriate. If shares of Stock are withheld to satisfy an applicable withholding requirement, the shares of Stock withheld shall have a Market Value on the date the tax is to be determined equal to the minimum statutory total tax (or tax calculated at such higher rates as determined by the Committee) which could be imposed on the transaction.

10.8. Company Certificate of Incorporation and Bylaws; Other Company Policies. This Plan and all Awards granted hereunder are subject to the certificate of incorporation and bylaws of the Company, as they may be amended from time to time, and all other Company policies duly adopted by the Board, the Committee or any other committee of the Board and as in effect from time to time regarding the acquisition, ownership or sale of Stock by officers, employees, directors, consultants, advisors and other service providers, including, without limitation, policies intended to limit the potential for insider trading and to avoid or recover compensation payable or paid on the basis of inaccurate financial results or statements, employee conduct, and other similar events.

10.9. Action Required upon Grant of an Award. Promptly following the grant of an Award, the Company shall, in accordance with NASDAQ Rule 5635(c), (a) issue a press release disclosing the material terms of the Award, including the recipient(s) of the Award and the number of shares of Stock involved and (b) provide written notice to the NASDAQ of the grant.

11. Reservation of Stock

The Company shall at all times during the term of the Plan and any outstanding Awards granted hereunder reserve or otherwise keep available such number of shares of Stock as will be sufficient to satisfy

the requirements of the Plan (if then in effect) and the Awards and shall pay all fees and expenses necessarily incurred by the Company in connection therewith.

12. Limitation of Rights in Stock; No Special Service Rights

A Participant shall not be deemed for any purpose to be a stockholder of the Company with respect to any of the shares of Stock subject to an Award, unless and until a certificate shall have been issued therefor and delivered to the Participant or his agent, or the Stock shall be issued through the direct registration system of the Company's transfer agent. Any Stock to be issued pursuant to Awards granted under the Plan shall be subject to all restrictions upon the transfer thereof which may be now or hereafter imposed by the certificate of incorporation and the bylaws of the Company. Nothing contained in the Plan or in any Award Agreement shall confer upon any recipient of an Award any right with respect to the continuation of his or her employment or other association with the Company (or any Affiliate), or interfere in any way with the right of the Company (or any Affiliate), subject to the terms of any separate employment or consulting agreement or provision of law or certificate of incorporation or bylaws to the contrary, at any time to terminate such employment or consulting agreement or to increase or decrease, or otherwise adjust, the other terms and conditions of the recipient's employment or other association with the Company and its Affiliates.

13. Unfunded Status of Plan

The Plan is intended to constitute an "unfunded" plan for incentive compensation, and the Plan is not intended to constitute a plan subject to the provisions of the Employee Retirement Income Security Act of 1974, as amended. With respect to any payments not yet made to a Participant by the Company, nothing contained herein shall give any such Participant any rights that are greater than those of a general creditor of the Company. In its sole discretion, the Committee may authorize the creation of trusts or other arrangements to meet the obligations created under the Plan to deliver Stock or payments with respect to Awards hereunder, provided, however, that the existence of such trusts or other arrangements is consistent with the unfunded status of the Plan.

14. Nonexclusivity of the Plan

Neither the adoption of the Plan by the Board nor any action taken in connection with the adoption or operation of the Plan shall be construed as creating any limitations on the power of the Board to adopt such other incentive arrangements as it may deem desirable, including without limitation, the granting of stock options and restricted stock other than under the Plan, and such arrangements may be either applicable generally or only in specific cases.

15. No Guarantee of Tax Consequences

It is intended that all Awards shall be granted and maintained on a basis which ensures they are exempt from, or otherwise compliant with, the requirements of Section 409A of the Code, pertaining non-qualified plans of deferred compensation, and the Plan shall be governed, interpreted and enforced consistent with such intent. However, neither the Company nor any Affiliate, nor any director, officer, agent, representative or employee of either, guarantees to the Participant or any other person any particular tax consequences as a result of the grant of, exercise of rights under, or payment in respect of an Award, including but not limited to that the provisions and penalties of Section 409A of the Code will or will not apply and no person shall have any liability to a Participant or any other party if a payment under an Award that is intended to benefit from favorable tax treatment or avoid adverse tax treatment fails to realize such intention or for any action taken by the Board or the Committee with respect to the Award.

16. Termination and Amendment of the Plan

16.1. Termination or Amendment of the Plan. Subject to the limitations contained in Section 16.3 below, including specifically the requirement of stockholder approval, if applicable, the Committee may at any time suspend or terminate the Plan or make such modifications of the Plan as it shall deem advisable. Unless the Committee otherwise expressly provides, no amendment of the Plan shall affect the terms of any Award outstanding on the date of such amendment.

16.2. Termination or Amendment of Outstanding Awards; Assumptions. Subject to the limitations contained in Section 16.3 below, including specifically the requirement of stockholder approval, if applicable, the Committee may at any time:

(a) amend the terms of any Award theretofore granted, prospectively or retroactively, provided that the Award as amended is consistent with the terms of the Plan;

(b) within the limitations of the Plan, modify, extend or assume outstanding Awards or accept the cancellation of outstanding Awards or of outstanding stock options or other equity-based compensation awards granted by another issuer in return for the grant of new Awards for the same or a different number of shares of Stock and on the same or different terms and conditions (including but not limited to the exercise price of any Option); and

(c) offer to buy out for a payment in cash or cash equivalents an Award previously granted or authorize the recipient of an Award to elect to cash out an Award previously granted, in either case at such time and based upon such terms and conditions as the Committee shall establish.

16.3. Limitations on Amendments, Etc.

(a) Without the approval of the Company's stockholders, no amendment or modification of the Plan by the Committee may (i) change the description of the persons eligible for Awards or (ii) effect any other change for which stockholder approval is required by law or the rules of any relevant stock exchange. Awards may be made under the Plan that involve shares of Stock in excess of the number of shares then available for issuance under the Plan, provided no shares shall actually be issued pursuant to those Awards until the number of shares of Stock available for issuance under the Plan is sufficiently increased by an amendment of the Plan authorizing such increase.

(b) No action by the Board or the Committee pursuant to this Section 16 shall impair the rights of the recipient of any Award outstanding on the date of such amendment or modification of such Award, as the case may be, without the Participant's consent; *provided*, *however*, that no such consent shall be required (A) in the case of any amendment or termination of any outstanding Award that is permitted by any provision of this Plan that is set forth in Section 8, Section 9 or in any other section of this Plan that is not Section 16.2 or (B) if the Board or Committee, as the case may be, (i) determines in its sole discretion and prior to the date of any Change of Control that such amendment or alteration either is required or advisable in order for the Company, the Plan or the Award to satisfy any law or regulation, including without limitation the provisions of Section 409A of the Code, or to meet the requirements of or avoid adverse financial accounting consequences under any accounting standard, (ii) determines in its sole discretion and prior to the date of any Change of Control that such amendment or alteration is not reasonably likely to significantly diminish the benefits provided under the Award, or that any such diminution has been adequately compensated, or (iii) reasonably determines on or after the date of Change of Control that such amendment or alteration either is required or advisable in order for the Company, the Plan or the Award to satisfy any law or regulation, including without limitation the provisions of Section 409A of the Code.

17. Recoupment

Participants shall be subject to any clawback, recoupment or other similar policy adopted by the Board as in effect from time to time and Awards and any cash, shares of Stock or other property or amounts due, paid or issued to a Participant shall be subject to the terms of such policy, as in effect from time to time.

18. Notices and Other Communications

Any communication or notice required or permitted to be given under the Plan shall be in such form as the Committee may determine from time to time. If a notice, demand, request or other communication is required or permitted to be given in writing, then any such notice, demand, request or other communication hereunder to any party shall be deemed to be sufficient if contained in a written instrument delivered in person or duly sent by first class registered, certified or overnight mail, postage prepaid, or by facsimile with a confirmation copy by regular, certified or overnight mail, addressed or by facsimile, as the case may be, (i) if to the recipient of an Award, at his or her residence address last filed with the Company and (ii) if to the Company, at its principal place of business, addressed to the attention of its Treasurer, or to such other address or facsimile number, as the case may be, as the addressee may have designated by notice to the addressor. All such notices, requests, demands and other communications shall be deemed to have been received: (i) in the case of personal delivery, on the date of such delivery; (ii) in the case of mailing, when received by the addressee; and (iii) in the case of facsimile transmission, when confirmed by facsimile machine report.

19. Stockholder Approval Not Required

It is expressly intended that approval of the Company's stockholders not be required as a condition of the effectiveness of the Plan, and the Plan's provisions shall be interpreted in a manner consistent with such intent for all purposes. Specifically, NASDAQ Rule 5635(c) generally requires stockholder approval for equity compensation plans adopted by companies whose securities are listed on the NASDAQ Stock Market that provide for the delivery of equity securities to any employees, directors or other service providers of such companies as compensation for services. NASDAQ Rule 5635(c)(4) provides an exemption in certain circumstances for employment inducement awards. Notwithstanding anything to the contrary herein, in accordance with NASDAQ Rule 5635(c)(4), Awards may only be granted as material inducements to Eligible Individuals being hired or rehired as employees, as applicable, and must be approved by (a) the Board, acting through a majority of the Company's Independent Directors or (b) the independent Compensation Committee of the Board. Accordingly, pursuant to NASDAQ Rule 5635(c)(4), the issuance of Awards and the Shares issuable upon exercise or vesting of such Awards pursuant to the Plan is not subject to the approval of the Company's stockholders.

20. Governing Law

The Plan and all Award Agreements and actions taken hereunder and thereunder shall be governed, interpreted and enforced in accordance with the laws of the State of Delaware, without regard to the conflict of laws principles thereof.

[End of document.]

RHYTHM PHARMACEUTICALS, INC.
2022 EMPLOYMENT INDUCEMENT PLAN

STOCK OPTION AGREEMENT

THIS STOCK OPTION AGREEMENT, dated as of _____, 20__ (this "Agreement"), is between Rhythm Pharmaceuticals, Inc., a corporation organized under the laws of the State of Delaware (the "Company"), and the individual identified in paragraph 1 below, currently residing at the address set out at the end of this Agreement (the "Optionee"). Capitalized terms used in this Agreement without definition shall have the respective meaning ascribed to such capitalized terms in the Plan (as defined below).

1. Grant of Option. Pursuant and subject to the Company's 2022 Employment Inducement Plan (as the same may be amended from time to time, the "Plan"), the Company grants to you, the Optionee identified in the table below, an option (the "Option") to purchase from the Company all or any part of a total of the number of shares identified in the table below (the "Optioned Shares") of the common stock, par value $0.001 per share, in the Company (the "Stock"), at the exercise price per share set out in the table below.

Optionee	_____
Number of Shares	_____
Exercise Price Per Share	_____
Grant Date	_____
Expiration Date	_____

2. Character of Option. This Option is not intended to be treated as an "incentive stock option" within the meaning of Section 422 of the Internal Revenue Code of 1986, as amended.

3. Expiration of Option. This Option shall expire at 5:00 p.m. EST on the Expiration Date or, if earlier, the earliest of the dates specified in whichever of the following applies:

a) If the termination of your employment or other association is on account of your death or disability, the first anniversary of the date your employment ends.

b) If the termination of your employment or other association is due to any other reason, three (3) months after your employment or other association ends.

4. Exercise of Option.

a) You may exercise this Option, in full or in part and at any time prior to the date this Option expires, as to the number of Optioned Shares for which this Option shall have become exercisable (the "Vested Shares") pursuant Section 4(b) below. However, during any period that this Option remains outstanding after the end of your association with the Company

and its Affiliates in any and all capacities as an officer, director, employee and/or consultant of the Company and its Affiliates, you may exercise it only to the extent of any remaining Vested Shares determined as of the effective time of the end of such association. The procedure for exercising this Option is described in Section 7.1(e) of the Plan; provided that in no event shall a fraction of a share of Stock be purchasable or deliverable upon exercise.

b) [Vesting terms to be inserted]

c)

Number of Shares in Each Installment	Initial Exercise Date for Shares in Installment

5. Transfer of Option. You may not transfer this Option except by will or the laws of descent and distribution, and, during your lifetime, only you may exercise this Option.

6. Incorporation of Plan Terms. This Option is granted subject to all of the applicable terms and provisions of the Plan, including but not limited to the limitations on the Company's obligation to deliver Optioned Shares upon exercise set forth in Section 9 therein.

7. Tax Consequences. The Company makes no representation or warranty as to the tax treatment to you of your receipt or exercise of this Option or upon your sale or other disposition of the Optioned Shares. You should rely on your own tax advisors for such advice.

8. Treatment as Wages or Compensation. No amounts paid or payable in connection with this Option shall constitute wages or compensation for purposes of any applicable law, if ever, prior to the date on which such amount has been earned, vested and become payable in accordance with the terms of this Agreement and the Plan. No such amount shall be treated as wages or compensation for purposes of any employee or other benefit plan of the Company and its Affiliates except to the extent and at the time provided in the respective employee or other benefit plan.

9. Acknowledgements. You acknowledge that you have reviewed and understand the Plan and this Agreement in their entirety, and have had an opportunity to obtain the advice of counsel prior to executing this Agreement. You hereby agree to accept as binding, conclusive and final all decisions or interpretations of the Committee upon any questions arising under the Plan or this Agreement.

10. Further Assurances. The parties agree to execute such further instruments and to take such action as may reasonably be necessary to carry out the intent of this Agreement.

11. Community Property. Without prejudice to the actual rights of the spouses as between each other, for all purposes of this Agreement, you shall be treated as agent and attorney-in-fact for that interest held or claimed by your spouse with respect to this Option and any Optioned

Shares and the parties hereto shall act in all matters as if the Optionee was the sole owner of this Option and (following exercise) any such Optioned Shares. This appointment is coupled with an interest and is irrevocable.

12. Miscellaneous.

a) This Agreement shall be construed and enforced in accordance with the laws of the State of Delaware, without regard to the conflict of laws principles thereof and shall be binding upon and inure to the benefit of any successor or assign of the Company and any executor, administrator, trustee, guardian, or other legal representative of you. Capitalized terms used but not defined herein shall have the meaning assigned under the Plan. This Agreement may be executed in one or more counterparts all of which together shall constitute but one instrument. In making proof of this Agreement it shall not be necessary to produce or account for more than one such counterpart.

b) The Option granted hereunder is intended to constitute an "employment inducement award" under NASDAQ Rule 5635(c)(4) that is exempt from the requirements of shareholder approval of equity compensation plans under NASDAQ Rule 5635(c)(4). This Agreement and the terms and conditions of the option granted hereunder will be interpreted consistent with such intent.

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

RHYTHM PHARMACEUTICALS, INC.
2022 EMPLOYMENT INDUCEMENT PLAN

OPTION EXERCISE FORM

Rhythm Pharmaceuticals, Inc.
500 Boylston Street, 11th Floor
Boston, MA 02116

Attention: Controller

Dear Sir:

In accordance with, and subject to the terms and conditions of, the Rhythm Pharmaceuticals, Inc. 2022 Employment Inducement Plan, as amended and in effect to date, I hereby elect to exercise my option granted under the agreement dated _____, to purchase _____ shares of the common stock, par value $0.001 per share, in Rhythm Pharmaceuticals, Inc. (the "Company").

Enclosed herewith is payment to the Company in the amount of $_____ in full payment of the option price of $_____ per share, for said shares.

Sincerely yours,

_____
Name:

RHYTHM PHARMACEUTICALS, INC.
2022 EMPLOYMENT INDUCEMENT PLAN

Restricted Stock Unit Agreement

This Restricted Stock Unit Agreement (this "Agreement"), dated as of _____, 20__ (the "Date of Grant"), is between Rhythm Pharmaceuticals, Inc., a corporation organized under the laws of the State of Delaware (the "Company") and _____ (the "Participant"). Capitalized terms used in this Agreement without definition shall have the respective meaning ascribed to such capitalized terms in the Rhythm Pharmaceuticals, Inc. 2022 Employment Inducement Plan (as the same may be amended from time to time, the "Plan").

1. Grant of Restricted Stock Units. Subject to the terms and conditions set forth in this Agreement and in the Plan, the Company hereby grants the Participant _____ Restricted Stock Units, subject to the restrictions set forth below and in the Plan (the "Stock Units"). Each Stock Unit represents the right of the Participant to receive a share of common stock of the Company ("Stock"), an amount of cash based on the value of a share of Stock, or any combination of the foregoing, as determined by the Committee, if and when the specified conditions are met in Section 4 below, and on the applicable settlement date set forth in Section 6 below.

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

3. Employment Inducement Award. The Stock Units are intended to constitute an "employment inducement award" under NASDAQ Rule 5635(c)(4) that is exempt from the requirements of stockholder approval of equity compensation plans under NASDAQ Rule 5635(c)(4). This Agreement and the terms and conditions of the Stock Units will be interpreted consistent with such intent.

4. Vesting.

a) As of the date of this Agreement, all of the Stock Units shall be unvested and subject to a Risk of Forfeiture pursuant to Section 5 below.

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

c) The vesting of the Stock Units shall be cumulative, but shall not exceed 100% of the Stock Units. If the foregoing schedule would produce fractional Stock Units, the number of Stock Units that vest shall be rounded down to the nearest whole Stock Unit and the fractional Stock Units will be accumulated so that the resulting whole Stock Units will be included in the number of Stock Units that become vested on the last Vesting Date.

d) Except as otherwise provided in a written employment agreement or severance agreement entered into by and between the Participant and the Company or an Affiliate thereof, in the event of a Change of Control before all of the Stock Units vest in accordance with Section 4(a) above, the applicable provisions of the Plan shall apply to the Stock Units, and the Committee may take such actions as it deems appropriate pursuant to the Plan.

e) Those Stock Units that vest pursuant to this Section 4 or pursuant to any action taken by the Committee pursuant to the Plan shall become free from the Risk of Forfeiture pursuant to Section 5 below.

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

6. Settlement of Stock Units and Tax Withholding.

a) If a Stock Unit vests in accordance with the provisions of Section 4 above, then, subject to the provisions of this Section 6(a) and Sections 6(b), 6(c) and 13 below, the Company shall issue to the Participant one share of Stock for such vested Stock Unit, or an amount of cash based on the value of a share of Stock for each vested Stock Unit, or a combination of the foregoing, as determined by the Committee, subject to applicable tax withholding obligations, as soon as reasonably practicable after the Vesting Date applicable to such vested Stock Unit. Notwithstanding anything express or implied in the foregoing provisions of this Section 6(a) to the contrary, in no event shall settlement of a vested Stock Unit occur later than the fifteenth day of the third calendar month following the calendar year in which the Vesting Date applicable to such vested Stock Unit occurs, and in no event shall Participant be permitted, directly or indirectly, to designate the calendar year of payment.

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

c) The obligation of the Company to deliver Stock shall also be subject to the condition that if at any time the Board shall determine in its discretion that the listing, registration or qualification of any shares of Stock upon any securities exchange or under any state or federal law, or the consent or approval of any governmental regulatory body is necessary or desirable as a condition of, or in connection with, the issuance of such shares, such shares may not be issued in whole or in part unless such listing, registration, qualification, consent or approval shall have been effected or obtained free of any conditions not acceptable to the Board. The issuance of shares of Stock, if any, to the Participant pursuant to this Agreement is subject to any applicable laws or regulations of the United States or of any state, municipality or other country having jurisdiction thereof.

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

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

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

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

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

12. Notice. Any notice to the Company provided for in this instrument shall be addressed to the Company, at the Company's principal place of business, addressed to the attention of the Company's Treasurer, and any notice to the Participant shall be addressed to such Participant at his or her residence address last filed with the Company. Any notice shall be delivered in accordance with Section 18 of the Plan.

13. Application of Section 409A of the Code. This Agreement is intended to be exempt from or otherwise comply with the provisions of Section 409A of the Code. Notwithstanding the foregoing, if any Stock Units constitute "deferred compensation" under Section 409A of the Code and such Stock Units become vested upon the Participant's termination of employment (or other association), settlement of such vested Stock Units shall be delayed for a period of six (6) months after the Participant's termination of employment (or other association) if the Participant is a "specified employee" as defined under Section 409A of the Code and if required pursuant to Section 409A of the Code. If settlement of any Stock Units is delayed in accordance with the foregoing provisions of this Section 13, such Stock Units shall be settled and paid within thirty (30) days after the date that is six (6) months following the Participant's termination of employment (or other association). To the extent subject to Section 409A of the Code, settlement of the Stock Units may only be made in a manner and upon an event permitted by Section 409A of the Code, and each settlement of the Stock Units shall be treated as a separate payment, and the right to a series of installment payments under the Stock Units shall be treated as a right to a series of separate payments. In no event shall the Participant, directly or indirectly, designate the calendar year of payment. The Company may change or modify the terms of this Agreement without the Participant's consent or signature if the Company determines, in its sole discretion, that such change or modification is necessary for purposes of compliance with or exemption from the requirements of Section 409A of the Code or any regulations or other guidance issued thereunder. Notwithstanding the previous sentence, the Company may also amend the Plan or this Agreement or revoke the Stock Units to the extent permitted by the Plan.

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

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

RHYTHM PHARMACEUTICALS, INC.	**FIRST_NAME LAST_NAME**
By: Signature	Signature of Participant
Title:	:
Participant's Address:	
	ADDRESS_LINE_1 ADDRESS_LINE_2 CITY, STATE ZIPCODE

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

Exhibit 10.6

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 $47,500 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	$ 35,000
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 40,000 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 20,000 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.

[***] Certain information in this document has been excluded pursuant to Regulation S-K, Item (601)(b)(10). Such excluded information is both (i) not material and (ii) the type that the Registrant treats as private or confidential.

CONFIDENTIAL
Execution Copy

EXCLUSIVE LICENSE AGREEMENT

THIS EXCLUSIVE LICENSE AGREEMENT (this "Agreement") effective as of December 3, 2021 (the "Effective Date"), is entered into between Rhythm Pharmaceuticals Inc., a corporation organized under the laws of Delaware ("Rhythm"), with a place of business at 222 Berkeley Street, 12th Floor, Boston, MA, USA, and RareStone Group Ltd., a limited company registered in Grand Cayman ("RareStone"), with a place of business at with its registered office at PO Box 472, 2nd Floor, Harbour Place, 103 South Church Street, George Town, Grand Cayman KY1-1106.

BACKGROUND

A. Rhythm has developed a compound known as IMCIVREE™ (setmelanotide) and owns or controls certain patents, know-how and other intellectual property relating thereto; and

B. RareStone and Rhythm wish to enter into an agreement whereby Rhythm will grant to RareStone, and RareStone will obtain, certain exclusive rights and licenses under such patents, know-how and other intellectual property to research, Develop, and Commercialize IMCIVREE™ for the diagnosis, treatment or prevention of conditions and diseases in humans in the greater China region, all on the terms and conditions set forth herein and therein.

AGREEMENT

NOW, THEREFORE, in consideration of the foregoing premises and the mutual covenants herein contained, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties hereby agree as follows:

1. Definitions. For the purposes of this Agreement, the following terms have the respective meanings set forth below, and grammatical variations of such terms have corresponding meanings:

1.1 "Accounting Standards" means, with respect to a Party, its Sublicensees, or any of their respective Affiliates, generally accepted accounting principles ("GAAP") in the U.S.; in each case as consistently applied throughout the applicable Person.

1.2 "Affiliate" means, with respect to any Person, any other Person which directly or indirectly controls, is controlled by, or is under common control with, such Person. A Person shall be regarded as in control of another Person if it owns, or directly or indirectly controls, fifty percent (50%) or more of the voting stock or other ownership interest of the other Person, or if it directly or indirectly possesses the power to direct or cause the direction of the management and policies of the other Person by any means whatsoever.

1.3 "API" means an active material that provides pharmacological activity in a pharmaceutical or biologic product (excluding formulation components such as coatings, stabilizers, excipients or solvents, adjuvants or controlled release technologies).

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1.4 "Business Day" means any day, other than a Saturday or a Sunday, on which the banks in New York, New York and Shanghai, China are open for business.

1.5 "Clinical Studies" means any human clinical study with respect to the Licensed Product.

1.6 "Combination Product" means a pharmaceutical product that includes the Licensed Compound and at least one (1) additional API that is either co-formulated or administered through a single formulation or sold together as a single product and invoiced as one product.

1.7 "Commercialization" means, with respect to the Licensed Product, any and all processes and activities directed to selling, offering for sale (including any application for marketing and pricing and reimbursement approvals), distributing, detailing, marketing, advertising, promoting, packaging, storing, transporting, distributing, importing, and other commercial exploitation activities; provided, however, that Commercialization shall exclude Development and Manufacturing. "Commercialize" and "Commercializing" shall have their correlative meanings.

1.8 "Commercially Reasonable Efforts" means, with respect to a Party's Development or Commercialization of Licensed Product, that level of efforts and resources commonly dedicated in the pharmaceutical industry to the analogous development or commercialization activities of a product of similar commercial potential at a similar stage in its lifecycle, in each case, taking into account market potential and market size, issues of safety and efficacy, anticipated or actual product labeling, the competitiveness of alternative Third Party product in the marketplace, the nature and extent of expected and actual market exclusivity (patent protection and regulatory coverage), the expected and actual reimbursability, and pricing and product profile, the proprietary position, the then-current competitive environment for such product and the likely timing of such product's entry into the market, the regulatory environment and status of such product, and other relevant scientific, technical and commercial factors, in each case, as measured by the facts and circumstances at the time such efforts are due.

1.9 "Compliance Laws" means all applicable Laws in the RareStone Territory or the Rhythm Territory relating to (a) the prevention of bribery, corruption, fraud, or improper payments, money laundering or counter-terrorist financing, including the U.S. Foreign Corrupt Practices Act of 1977 (the "FCPA"), or (b) export controls, economic or financial sanctions or trade embargoes imposed, administered or enforced from time to time by any Governmental Authority.

1.10 "Competing Product" means any product, other than Licensed Product, that [***].

1.11 "Control" (including any variations such as "Controlled" and "Controlling"), in the context of intellectual property rights, data, Registrations and/or other information or assets, means that such Party or its Affiliate owns or possesses rights to such

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intellectual property rights, data, Registrations and/or other information or assets, as applicable, sufficient to grant the applicable license or sublicense under this Agreement, without violating the terms of an agreement with a Third Party.

1.12 "CTA" means a Clinical Trial Authorization application filed with the NMPA for authorization to commence Clinical Studies.

1.13 "Data" mean any and all pharmacology data, preclinical data, clinical data, including raw data, as well as marketing, market access, pharmacovigilance and other data pertaining to the Licensed Product, in each case to the extent Controlled by a Party as of the Effective Date or during the Term of this Agreement.

1.14 "Development" means pre-clinical and clinical research and drug development activities, including but not limited to toxicology, pharmacology, statistical analysis, Clinical Studies (including pre- and post-approval studies), regulatory affairs, and regulatory activities pertaining to designing and carrying out Clinical Studies and obtaining Registrations; provided, however, that Development shall exclude Manufacturing and Commercialization. "Develop" and "Developing" shall have their correlative meanings.

1.15 "Distributor" means a Third Party whom RareStone, its Affiliates or a Sublicensee engages to offer for sale, sell and/or import Licensed Products purchased from RareStone, such Affiliate or such Sublicensee, as applicable, for resale by such Third Party under the label of RareStone, such Affiliate or such Sublicensee, as applicable (provided, however, that such resale may be under the label of such Third Party in a jurisdiction if a local entity is required to obtain a label in such jurisdiction); provided that the term "Distributor" shall not include any person or entity who pays RareStone, its Affiliate or a Sublicensee any consideration (in any form) with respect to such engagement other than the consideration paid for the purchase of such Licensed Products, such person or entity being deemed a Sublicensee hereunder.

1.16 "Drug Product" means the formulation of the Licensed Compound approved by the applicable Regulatory Authority including Setmelanotide and any excipients, agents, and non-active ingredients, in any formulation or dosage form.

1.17 "Drug Substance" means Setmelanotide.

1.18 "FDA" means the United States Food and Drug Administration, or any successor entity thereto.

1.19 "Field" means the diagnosis, treatment or prevention of conditions and diseases in humans.

1.20 "First Commercial Sale" means the first sale of Licensed Product in the RareStone Territory by any of RareStone, its Sublicensees or its or their respective Affiliates to a Third Party after Registration (if required) of Licensed Product.

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1.21 "Generic Product" means a prescription pharmaceutical product sold by a Third Party that [***].

1.22 "Global Phase III Clinical Trial" means Rhythm's multi-site, multi-national Phase III Clinical Trial anticipated by the Parties to be the basis of a Registration, as further described in the Clinical Development Plan.

1.23 "Governmental Authority" means any (a) nation, state, commonwealth, province, territory, county, municipality, district or other jurisdiction of any nature; (b) international, multinational, federal, state, local, municipal, foreign or other government, agency or authority; or (c) governmental or quasi-governmental authority of any nature (including any governmental division, department, agency, commission, securities exchange or instrumentality and any court or other tribunal).

1.24 "Joint Development Committee" or "JDC" means the joint development committee comprising representatives of Rhythm and RareStone, described in Section 6.

1.25 "Joint Steering Committee" or "JSC" means the joint steering committee, comprising representatives of Rhythm and RareStone, described in Section 6.

1.26 "Know-How" means all inventions, discoveries, data, information (including scientific, technical or regulatory information), trade secrets, processes, means, methods, practices, formulae, instructions, procedures, techniques, materials, technology, results, analyses, designs, drawings, computer programs, apparatuses, specifications, technical assistance, laboratory, pre-clinical and clinical data (including laboratory notes and notebooks), and other material or know-how, in written, electronic or any other form, whether or not confidential, proprietary or patentable, including without limitation: development technology; biology, chemistry, pharmacology, toxicology, drug stability, manufacturing and formulation, test procedures, synthesis, purification and isolation techniques, quality control data and information, methodologies and techniques; information regarding clinical and non-clinical safety and efficacy studies, including study designs and protocols, marketing studies, absorption, distribution, metabolism and excretion studies; assays and biological methodology.

1.27 "Knowledge of Rhythm" or "Rhythm's Knowledge" means the actual knowledge of any of [***].

1.28 "Laws" or "Law" means any applicable federal, national, supranational, state, provincial, local or other domestic or foreign law, statute, treaty, rule, regulation, order, directive, ordinance, interpretation, or policy (including any Governmental Authority written guidance for industry) with or by, or any other requirement issued, enacted, adopted, promulgated, implemented or otherwise put into effect by or under the authority of any Governmental Authority that apply to a Party and its activities hereunder.

1.29 "Licensed Compound" means the acetate salt form of Setmelanotide and the chloride salt form of Setmelanotide.

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1.30 "Licensed IP Rights" means the Licensed Patents, the Licensed Marks and the Licensed Know-How.

1.31 "Licensed Know-How" means any Know-How Controlled by Rhythm or its Affiliates as of the Effective Date or during the Term thereof that is necessary or reasonably useful to Develop, Manufacture, or Commercialize the Licensed Product in the Field in the RareStone Territory.

1.32 "Licensed Marks" means the product-specific Trademarks Controlled by Rhythm or any of its Affiliates as of the Effective Date and intended for use in connection with the packaging and labeling of Licensed Product, as listed on Exhibit A, any other product-specific Trademarks Controlled by Rhythm or any of its Affiliates after the Effective Date and intended for use in connection with the packaging and labeling of Licensed Product, which are accepted in writing by RareStone for use in the RareStone Territory (which shall be added to Exhibit A promptly after such acceptance), and any other product-specific Trademarks that Rhythm and RareStone mutually agree upon for use with the Licensed Product in the RareStone Territory during the Term of this Agreement.

1.33 "Licensed Patents" means any and all Patents Controlled by Rhythm or its Affiliates as of the Effective Date or during the Term that claim inventions that are necessary or reasonably useful to Develop, Manufacture or Commercialize the Licensed Product in the Field in the RareStone Territory, including the Patents listed on Exhibit B.

1.34 "Licensed Product" means any pharmaceutical product that contains the Licensed Compound, including any Combination Products (excluding, for clarity, any Combination Products that include any APIs claimed or covered by intellectual property rights Controlled by Rhythm, other than the Licensed Compound).

1.35 "Licensed Technology" means the Licensed Patents and the Licensed Know-How.

1.36 "Manufacture" means activities directed to manufacturing, processing, packaging, labeling, filling, finishing, assembly, shipping, storage, or freight of any pharmaceutical or biologic product (or any components or process steps involving any product or any companion diagnostic), placebo, or comparator agent, as the case may be, including quality assurance and stability testing, characterization testing, quality control release testing of drug substance and drug product, quality assurance batch record review and release of product, process development, qualification, and validation, scale-up, pre-clinical, clinical, and commercial manufacture and analytic development, and product characterization; provided, however, that Manufacture shall exclude Development and Commercialization. "Manufacturing" and "Manufactured" shall have their correlative meanings.

1.37 "Manufacturing Cost" means, with respect to the supply of Licensed Product by an unaffiliated Third Party, the direct acquisition cost paid by Rhythm for such Licensed Product, and, with respect to the supply of Licensed Product Manufactured directly by

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Rhythm or its Affiliates, the fully burdened manufacturing costs applicable to the supply of the Licensed Product, which manufacturing costs: [***].

1.38 "Marketing Authorization Application" or "MAA" means any drug marketing authorization or similar application, including all supplements and amendments thereto, filed with the NMPA or other applicable Regulatory Authority, which is required to Commercialize the Licensed Product in the RareStone Territory.

1.39 "NMPA" means the National Medical Products Administration of China (formerly known as the China Food and Drug Administration (CFDA)), or any successor thereto.

1.40 "Net Sales" means the gross amounts invoiced by RareStone, its Sublicensees, or any of their respective Affiliates (in each case, a "Selling Party") for sales or other dispositions of Licensed Product to Third Parties (other than another Selling Party, unless such Selling Party is the end user of the applicable Licensed Product), less the following amounts actually incurred, allowed, paid and accrued:

(a) [***];

(b) [***];

(c) [***];

(d) [***];

(e) [***];

(f) [***]; and

(g) [***];

provided that, in each case (a) through (g), (i) each such deduction is calculated in a manner consistent with the Selling Party's applicable Accounting Standards, consistently applied by the Selling Party, and (ii) each such deduction is directly allocable to Licensed Product, or apportioned on a good faith, fair and equitable basis to Licensed Product and other products of the Selling Party and its Affiliates such that Licensed Product does not bear a disproportionate portion of such deductions, and (iii) no particular amount identified above shall be deducted more than once in calculating Net Sales (i.e., no "double counting" of deductions).

For clarification, sale or other disposition of Licensed Product by a Selling Party to another Selling Party for resale by such other Selling Party to a Third Party (other than a Selling Party) shall not be deemed a sale for purposes of this definition of "Net Sales," provided that the subsequent resale is included in the computation of Net Sales. In the event of any sale or other disposition of Licensed Product for any consideration other than exclusively monetary consideration on bona fide arm's-length terms (including any sale or other disposition of Licensed Product by a Selling Party to another Selling Party for end use by such other Selling

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Party), then for purposes of calculating Net Sales under this Agreement, such Licensed Product shall be deemed to have been sold exclusively for cash [***].

[***].

Net Sales for a Combination Product in the RareStone Territory will mean the gross amount attributable to the Combination Product less the deductions set forth in clauses (a) – (g) above, to the extent applicable and subject to the limitations set forth above, multiplied by [***]:

(a) [***];

(b) [***];

(c) [***]; or

(d) [***].

1.41 "Patent(s)" means any and all patents and patent applications of any kind, together with all provisional applications, additions, divisions, continuations, continued prosecution applications, continuations-in-part, substitutions, confirmations, validations, reissues, re-examinations, *inter partes* reviews, registrations, patent term extensions, supplemental protection certificates, restoration and renewals of any of the foregoing in any jurisdiction in the world.

1.42 "Party" means Rhythm or RareStone, individually; and "Parties" means Rhythm and RareStone, collectively.

1.43 "Payment Period" means on a Region-by-Region basis, the period of time beginning on the date of the First Commercial Sale of Licensed Product in such Region and ending upon the latest of (a) the expiration of the last to expire Licensed Patent in such Region having a Valid Claim that covers such Licensed Product; (b) the loss of Regulatory Exclusivity for the Licensed Product in such Region; or (c) [***] following the date of the First Commercial Sale of the first Licensed Product by RareStone, its Affiliates or Sublicensees in such Region.

1.44 "Person" means any individual, partnership, firm, corporation, association, trust, unincorporated organization or other entity, as well as any syndicate or group of any of the foregoing.

1.45 "Phase III Clinical Trial" means a pivotal clinical trial in humans performed to gain evidence with statistical significance of the efficacy of a product in a target population, and to obtain expanded evidence of safety for such product that is needed to evaluate the overall benefit-risk relationship of such product, to form the basis for the filing for Registration and to provide an adequate basis for physician labeling, as further described in 21 C.F.R. § 312.21(c), or its foreign equivalent (including any such clinical study in any country other than the United States), regardless of whether such trial is labeled as a Phase III Clinical Trial.

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1.46 "RareStone Product Know-How" means Know-How Controlled by RareStone that are necessary or reasonably useful to Develop, Manufacture, or Commercialize the Licensed Product in the Field in the RareStone Territory, but excluding the Licensed Know-How.

1.47 "RareStone Territory" means Greater China, including mainland China, Hong Kong, and Macao.

1.48 "Region" means each of (a) People's Republic of China, (b) Hong Kong Special Administration Region, (c) Macau Special Administration Region, and (d) Taiwan, if incorporated into the RareStone Territory by amendment.

1.49 "Registered IP Rights" means the Licensed Patents and the Licensed Marks within the RareStone Territory.

1.50 "Registration" means, with respect to the Licensed Product in any country or jurisdiction, any and all registrations, licenses, permits or governmental approvals, certifications or clearances from any Regulatory Authority necessary, under applicable Law in a country or other jurisdiction, for the purchase, distribution, commercialization, manufacture, promotion, marketing or sale of the Licensed Product in any such country or jurisdiction. "Register" or "Registering" shall have their correlative meanings.

1.51 "Regulatory Authority" means the NMPA or any other regulatory body with similar regulatory authority within the RareStone Territory or in any jurisdiction outside the RareStone Territory.

1.52 "Regulatory Exclusivity" means any exclusive marketing rights or data exclusivity rights conferred by any applicable Regulatory Authority in the RareStone Territory, other than an issued and unexpired Patent, including any regulatory data protection exclusivity (including, where applicable, pediatric exclusivity and/or orphan drug exclusivity) and/or any exclusivity afforded by restrictions on the granting by a Regulatory Authority of regulatory approval to market a Generic Product in the RareStone Territory.

1.53 "Regulatory Filing" means any Marketing Authorization Application, or any other licenses, applications, registrations, notifications, submissions and authorizations made to or received from a Regulatory Authority in a jurisdiction necessary to obtain a Registration for the development, manufacture and/or commercialization of a human pharmaceutical product, together with all amendments and supplements to any of the foregoing.

1.54 "Rhythm Territory" means all countries in the world other than the RareStone Territory.

1.55 "Setmelanotide" means an 8-amino acid cyclic peptide, as further described in Exhibit C.

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1.56 "Sublicense" means an agreement that directly or indirectly grants a sublicense, immunity or other right under the Licensed Technology to Develop, Manufacture, Commercialize, or otherwise exploit the Licensed Product, in the RareStone Territory, pursuant to Section 2.4.

1.57 "Sublicensee" means a RareStone Affiliate or a Third Party with whom RareStone has granted or otherwise entered into a Sublicense, provided such Sublicense has not expired or been terminated. Notwithstanding the foregoing, Sublicensees shall not include Distributors.

1.58 "Tax" or "Taxes" means any and all federal, state, local and foreign taxes, assessments and other governmental charges, duties, impositions and liabilities that are specific to the sale of the Licensed Products, including taxes based upon or measured by gross receipts, income, profits, sales, use and occupation, and value added, ad valorem, transfer, franchise, and property taxes together with all interest, penalties and additions imposed with respect to such amounts.

1.59 "Third Party" means any Person other than RareStone, Rhythm or their respective Affiliates.

1.60 "Trademark" means all registered and unregistered trademarks, service marks, trade dress, trade names, logos, insignias, domain names, symbols, designs, and combinations thereof.

1.61 "Upstream Agreements" means any assignment or license agreement between Rhythm and a Third Party regarding the Licensed IP Rights, which includes, as of the Effective Date, [***].

1.62 "Valid Claim" means (a) a claim of an issued and unexpired Patent included within the Licensed Patents, which has not been held permanently revoked, unenforceable, abandoned, permanently lost through an interference or an opposition proceeding, or invalid by a final decision of a court or other governmental agency of competent jurisdiction, unappealable or unappealed within the time allowed for appeal, and which has not been admitted to be invalid or unenforceable through reissue or disclaimer or otherwise, or (b) a pending claim of a pending patent application included within the Licensed Patents that (i) has been asserted and continues to be prosecuted in good faith (provided, however, that if a claim of a pending patent application has not issued within five (5) years after the earliest filing date from which such claim takes priority, such claim shall no longer constitute a Valid Claim for the purposes of this Agreement from such 5th anniversary unless and until a patent issues with such claim) and (ii) has not been abandoned or finally rejected without the possibility of appeal or refiling.

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2. License Grant/Obligations.

2.1 Licenses

2.1.1 IP License. Subject to the terms and conditions of this Agreement, Rhythm hereby grants to RareStone an exclusive (even as to Rhythm), sublicenseable (subject to Section 2.4), royalty-bearing license under the Licensed Technology to Develop, Manufacture (solely to the extent set forth in Section 4.4), Commercialize, and otherwise exploit Licensed Products, and to obtain and maintain Registrations, in each case solely in the Field for use in the RareStone Territory.

2.2 Access to Licensed Know-How. Rhythm shall provide or make available to RareStone all Licensed Know-How that is necessary or reasonably useful for the Development and Registration of the Licensed Product and exists as of the Effective Date, which provision or access shall occur in a manner and following a reasonable schedule and plan agreed by the Parties. During the Term of this Agreement, Rhythm shall provide or make available to RareStone additional Licensed Know-How that is necessary or reasonably useful for the Development or Registration of the Licensed Product, to the extent that such Licensed Know-How comes to Rhythm's attention (or is reasonably requested by RareStone) and has not previously been provided or made available to RareStone. Without limiting the generality of the foregoing, Rhythm shall provide RareStone with a copy of the M3 module of the clinical trial dossier for the Licensed Product (or such portions as RareStone reasonably requests), as well as all supporting data, within [***] after the Effective Date.

2.3 Right of Reference. Subject to the terms and conditions of this Agreement, Rhythm hereby grants to RareStone an exclusive (including with respect to Rhythm), non-transferable (except in connection with a permitted assignment of this Agreement), right of reference under any and all Registrations and Regulatory Filings Controlled by Rhythm for the Licensed Product or its use, to Develop, obtain and maintain Registrations for, Manufacture (to the extent necessary in accordance with this Agreement), and Commercialize the Licensed Product in the RareStone Territory. RareStone shall have the right to grant further rights of reference, through multiple tiers, to Third Parties and Affiliates. Subject to the terms and conditions of this Agreement, RareStone hereby grants to Rhythm an exclusive (including with respect to RareStone), non-transferable (except in connection with a permitted assignment of this Agreement), right of reference under any and all Registrations and Regulatory Filings Controlled by RareStone for Licensed Product or its use, to Develop, obtain and maintain Registrations for, Manufacture, and Commercialize the Licensed Product outside the RareStone Territory. Rhythm shall have the right to grant further rights of reference, through multiple tiers, to Third Parties and Affiliates.

2.4 Sublicenses.

2.4.1 RareStone shall have the right, in accordance with this Section 2.4, to enter into a Sublicense with: (a) its Affiliates, without Rhythm's consent; or (b) a Third Party, with Rhythm's express prior written consent, for the purpose of Registering with Regulatory

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Authorities, Developing, Manufacturing or Commercializing the Licensed Product in each case jointly with, or for the benefit of, RareStone. RareStone may grant sublicenses hereunder to such Affiliates and Third Parties solely on the terms set forth in this Section 2.4.1 and Section 2.4.2 below.

2.4.2 Each Sublicense granted by RareStone pursuant to this Section 2.4 will be in writing and will be consistent with the relevant restrictions and limitations set forth in this Agreement. No Sublicense will diminish, reduce or eliminate any obligation of either Party under this Agreement. Any Sublicense entered into by RareStone pursuant to this Section 2.4 will contain the following provisions: (a) a requirement that such Sublicensee submit applicable sales or other reports to Rhythm consistent with the reporting requirements set forth in Section 7.7; (b) an audit requirement consistent with that set forth in Section 7.10; (c) a requirement that such Sublicensee comply with the confidentiality provisions and restrictions on use of Confidential Information contained in Article 9 with respect to Rhythm's Confidential Information; and (d) those provisions required by the Upstream Agreements. RareStone shall remain responsible for its obligations under this Agreement and will ensure that each of its Sublicensees complies with all relevant provisions of this Agreement. Promptly following the execution of each Sublicense to a Sublicensee, RareStone shall provide Rhythm with an executed copy of such Sublicense; provided, however, that RareStone shall have the right to redact any confidential terms from the copy provided to Rhythm.

2.5 RareStone's Right of First Negotiation. If at any time during the Term of this Agreement, Rhythm desires to enter into negotiations with any Third Party for the grant of a license or rights to Develop or Commercialize the Licensed Product in the Field solely in Taiwan ("ROFN Territory"), then, prior to entering into discussions or negotiations with any Third Party, Rhythm shall provide written notice to RareStone ("ROFN Notice") and offer to RareStone the first right to negotiate for the right or license to Develop or Commercialize the Licensed Product in the Field in the ROFN Territory ("ROFN"). RareStone shall have [***] after receiving the ROFN Notice to notify Rhythm in writing whether RareStone desires to exercise its ROFN. If RareStone notifies Rhythm that RareStone elects to exercise its ROFN, the Parties shall enter into exclusive good faith negotiations for a period of [***] (the "Negotiation Period") to include the ROFN Territory in the RareStone Territory, subject to mutual, written agreement of any financial consideration with respect to the ROFN Territory. If the Negotiation Period expires before the Parties have mutually agreed on the terms and conditions to include the ROFN Territory under this Agreement, Rhythm will have no additional obligations to negotiate with RareStone and Rhythm shall be free to Develop and Commercialize Licensed Product in the ROFN Territory, directly or through an Affiliate or an agreement with a Third Party, provided that, for the six months immediately following the expiration of such Negotiation Period, Rhythm shall not enter into any such agreement with any Third Party on terms that are more favorable to the Third Party than the last terms offered to RareStone during the Negotiation Period.

2.6 Activities Outside the RareStone Territory. To the extent permitted under applicable Law, RareStone agrees that neither it, nor any of its Affiliates, will sell or provide the Licensed Product to any Third Party and shall not allow its Sublicensees to sell or provide the

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Licensed Product to any Third Party, if RareStone or its relevant Affiliate or Sublicensee knows, or has reason to know, that Licensed Products sold or provided to such Third Party may be sold or transferred, directly or indirectly, for use in the Rhythm Territory.

2.7 Competing Product Activities in the RareStone Territory.

2.7.1 Until [***], RareStone covenants that neither it nor its Affiliates or permitted Sublicensees will, (i) grant or offer any license or otherwise enable or authorize any Third Party or (ii) conduct, either directly or indirectly, any activities, whether independently or with or for the benefit of a Third Party, in each case of (i) and (ii) with respect to the Development (including to obtain or maintain any regulatory approvals for), Manufacture, Registration, or Commercialization of any Competing Product in the RareStone Territory. On and after [***], in the event that RareStone or any of its Affiliates desires to (i) grant or offer any license or otherwise enable or authorize any Third Party or (ii) conduct, either directly or indirectly, any activities, whether independently or with or for the benefit of a Third Party, in each case of (i) and (ii) with respect to the Development (including to obtain or maintain any regulatory approvals for), Manufacture, Registration, or Commercialization of any Competing Product in the RareStone Territory, RareStone would so notify Rhythm in writing (a "Competing Product Notice"). By written notice to RareStone provided within [***], Rhythm shall have the right to elect to receive a royalty on Net Sales by RareStone, its Affiliates and their respective (sub)licensees of such Competing Product in the RareStone Territory. Rhythm shall have the right to receive up to a [***] royalty on such Net Sales, [***], as elected by Rhythm in such notice; provided, that the royalty payable under this Agreement with respect to Net Sales on Licensed Product in the RareStone Territory shall be decreased by a percentage equal to the percent rate selected by Rhythm with respect to such Competing Product.

2.7.2 Rhythm hereby covenants that, during the Term, neither it nor its Affiliates will, (i) grant or offer any license or otherwise enable or authorize any Third Party or (ii) conduct, either directly or indirectly, any activities, whether independently or with or for the benefit of a Third Party, in each case of (i) and (ii) with respect to the development (including to obtain or maintain any regulatory approvals for), manufacture, registration, promotion, advertisement or distribution of any Competing Product in the RareStone Territory.

2.8 Relevant In-Licensed IP. In the event that, RareStone desires to in-license from a Third Party Patents that cover the Licensed Product, it shall so notify Rhythm in writing. The Parties shall promptly confer in good faith with respect to the relevant Patents and discuss the need or desirability of taking a license thereto. Rhythm shall have the first right to obtain such license to such Patents worldwide, and shall confer in good faith with RareStone regarding the terms and conditions thereof to the extent relevant to the RareStone Territory. If Rhythm obtains a license to such Patents, Rhythm shall either obtain a license thereunder including the RareStone Territory on terms reasonably acceptable to RareStone, in which case RareStone shall be responsible for the portion of all payments due thereunder to the extent reasonably attributable to the RareStone Territory (in which case such payments borne by RareStone will be treated as if they were paid to a Third Party for purposes of Section 7.6.2), or otherwise Rhythm shall exclude from the scope of its license the RareStone Territory. If either Rhythm declines to take a

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license to such Third Party Patents, or excludes from any license it obtains under such Patents the RareStone Territory, then RareStone shall have the right to obtain such a license under such Patents solely for the RareStone Territory. If Rhythm elects to take a license to Third Party Patents under this Section 2.8 that includes the RareStone Territory, Rhythm shall provide to RareStone notice thereof, and upon RareStone's receipt of such notice (i) RareStone's such Third Party Patents will be included in the Licensed Patents and licensed to RareStone pursuant to Section 2.1 automatically, and are hereby granted as of the date of RareStone's receipt of such notice, and (ii) RareStone agrees to comply with any obligations of Rhythm under any such in-license agreement with respect to such Patents, that apply to RareStone and of which RareStone was informed in writing in advance by Rhythm, including any obligation to make payments for RareStone's use of the same.

3. Regulatory.

3.1 RareStone Diligence. During the Term, RareStone shall use Commercially Reasonable Efforts (whether alone or with or through its Sublicensees and its or their respective Affiliates) to Develop and Register the Licensed Products in the Field in the RareStone Territory, including without limitation for each indication for which Rhythm is eligible to receive milestone payments pursuant to Sections 7.3, [***].

3.2 Regulatory Strategy. RareStone shall be responsible for obtaining the initial Registration and any subsequent Registrations, as required, for the Licensed Product in the Field in the RareStone Territory [***]. RareStone shall develop and determine a regulatory strategy for the Licensed Product in the RareStone Territory, which strategy shall be subject to JSC's review and approval. The Parties initially agree as follows:

3.2.1 Rhythm shall initially hold any and all Regulatory Filings submitted to and Registrations granted by the NMPA for the Licensed Product Manufactured by Rhythm ("Imported Version of Product") until the Manufacturing Process has been transferred to RareStone, pursuant to Section 4.4, (such date, the "Regulatory Responsibility Transfer Date"), and Rhythm hereby designates RareStone as Rhythm's regulatory agent.

3.2.2 As Rhythm's regulatory agent, RareStone or one of its Affiliates shall be responsible for undertaking all regulatory activities and interactions with Regulatory Authorities in the RareStone Territory for the Imported Version of Product in Rhythm's name as the express and authorized regulatory agent of record for Rhythm in the RareStone Territory.

3.2.3 Following the Regulatory Responsibility Transfer Date, RareStone or one of its Affiliates will be responsible for all regulatory activities and interactions with the Regulatory Authorities in the RareStone Territory leading up to and including obtaining (to the extent not already obtained) and thereafter maintaining Registrations for such locally-Manufactured Licensed Product in the RareStone Territory, in RareStone's or its Affiliate's own name.

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3.3 RareStone Ownership. Following the Regulatory Responsibility Transfer Date, RareStone shall own any and all Regulatory Filings and Registrations for the Licensed Product in the Field in the RareStone Territory. Such Registrations shall be transferred to Rhythm in the circumstances set forth in Section 14.2.2.

3.4 Audit and Inspection. RareStone shall permit Rhythm to review RareStone's guidelines and procedures for (i) the receipt, investigation, recording, communication, and exchange (as between the Parties) of adverse event reports, pregnancy reports, and any other information concerning the safety of the Licensed Product (ii) the preparation, filing, prosecution, submission and control all Regulatory Filings for Licensed Product in the RareStone Territory and the communications with the NMPA and other Regulatory Authorities in the RareStone Territory regarding Regulatory Filings and Registration of Licensed Product.

3.5 Clinical Development Plan.

3.5.1 Promptly after the Effective Date, the Parties shall collaborate on a plan for the clinical Development of the Licensed Product in the RareStone Territory, which may be amended from time to time (the "Clinical Development Plan"). An initial outline of the Clinical Development Plan is attached as Exhibit D. The Parties shall use reasonable efforts to finalize and mutually agree on such Clinical Development Plan within [***] after the Effective Date. The Clinical Development Plan will include in reasonable detail any Development activities, as required, and associated timelines, for the Licensed Product in the RareStone Territory, including the Global Phase III Clinical Trial. Upon such mutual agreement, the Clinical Development Plan will be automatically added to Exhibit D to this Agreement.

3.5.2 The Parties shall prepare for the JDC's review updates of the Clinical Development Plan (as defined in Section 6.2.2(c)) for each year of the Term until Registration of the Licensed Product by or on behalf of RareStone, and in any event, the JDC shall review the then-current Clinical Development Plan [***] (or more frequently to address material issues arising within such time period) until such time.

3.5.3 The Parties hereby agree that all Development activities on the Licensed Product conducted by RareStone in the RareStone Territory under this Agreement shall be conducted pursuant to the Clinical Development Plan as reviewed and approved by the JDC.

3.6 Clinical Studies and Pre-Clinical Studies.

3.6.1 RareStone shall be responsible for conducting all activities in connection with the Global Phase III Clinical Trial, [***], solely to the extent such activities are necessary or reasonably useful to support Registration in the Field in the RareStone Territory. Notwithstanding the foregoing, RareStone's obligation to participate in such Global Phase III Clinical Trial in the RareStone Territory shall not exceed a maximum of [***] for such Global Phase III Clinical Trial, nor shall [***] to conduct activities in the RareStone Territory in connection with the Global Phase III Clinical Trial exceed [***].

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3.6.2 As between the Parties, RareStone shall be responsible, [***], for conducting, to the best of its ability, any and all Clinical Studies and/or preclinical studies (which may, in either case, require sites in the RareStone Territory), and all other regulatory activities, required for obtaining, supporting and maintaining Registrations in the RareStone Territory in accordance with the Clinical Development Plan.

3.6.3 Subject to the terms of this Agreement (including Section 3.6.1) and as between the Parties, RareStone shall be solely responsible (with input from Rhythm both through the JSC and otherwise), [***] for conducting all regulatory activities, whether pre-Registration or post-Registration of the locally-Manufactured Licensed Product, required for obtaining and maintaining Registration in the RareStone Territory of locally-Manufactured Licensed Product and in accordance with the Clinical Development Plan.

3.7 Regulatory Communications.

3.7.1 RareStone shall be responsible for and shall have the exclusive right, in consultation with Rhythm and subject to Rhythm's rights pursuant to Section 3.8, (a) to prepare, file, prosecute, submit and control all Regulatory Filings for Licensed Product in the RareStone Territory; (b) to interact and communicate with the NMPA and other Regulatory Authorities in the RareStone Territory regarding Regulatory Filings and Registration of Licensed Product; (c) to collect information on the adverse effects of Licensed Product and report the same to the NMPA and other Regulatory Authorities in the RareStone Territory; and (d) to coordinate and control any recall of Licensed Product in accordance with this Agreement and applicable Laws and regulations and reporting relevant information to the NMPA and other Regulatory Authorities in the RareStone Territory. Subject to the terms and conditions of this Agreement, [***].

3.7.2 As between the Parties, Rhythm shall be responsible and shall have the exclusive right to (a) to prepare, file, prosecute, submit and control all Regulatory Filings for Licensed Product in the Rhythm Territory; (b) to interact and communicate with the applicable Regulatory Authority for Licensed Product in such Rhythm Territory regarding Regulatory Filings and Registration of Licensed Product; (c) to collect information on the adverse effects of Licensed Product and report the same to the applicable Regulatory Authorities in the Rhythm Territory; and (d) to coordinate and control any recall of Licensed Product in accordance with this Agreement and applicable Laws and regulations and reporting relevant information to the applicable Regulatory Authorities in the Rhythm Territory.

3.8 Rhythm Review and Assistance. Within [***] of the Effective Date, Rhythm shall provide to RareStone the then-existing dossier for the Licensed Product and any materials or documents Controlled by Rhythm as necessary or reasonably useful to RareStone or required by Regulatory Authorities for the Registration of the Licensed Product in the RareStone Territory. Rhythm shall use Commercially Reasonable Efforts to execute such certificates and other instruments and documents readily available and its reasonable efforts to perform all such other acts as may be necessary or appropriate and otherwise cooperate with and provide reasonable assistance to RareStone as RareStone may request from time to time regarding any

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Regulatory Filings or amendments to Registrations for Licensed Product, including qualifying a Third Party second source of Licensed Product to the extent required by applicable Laws and regulations, in all cases, [***]. RareStone shall provide to Rhythm updates with respect to planned communications with Regulatory Authorities in the RareStone Territory, and submissions to such Regulatory Authorities, with respect to Licensed Products in the Field in the RareStone Territory. Without limiting the foregoing, Rhythm shall translate all Regulatory Filings and supporting data, information and material for the Rhythm Territory that are not in English into English [***] and shall provide such English translations to RareStone. RareStone shall be responsible, [***], to translate such data, information and material into Chinese as may be necessary to obtain and maintain Registrations in the RareStone Territory. RareStone shall keep Rhythm fully and promptly informed as to its progress and activities relating to the Development and Registration, including with respect to regulatory matters and meetings with Regulatory Authorities, by way of updates to the JSC at its meetings or as reasonably requested by Rhythm at any other time. RareStone agrees to consider in good faith all comments provided by Rhythm with respect to such Development and Registration of the Licensed Product for the RareStone Territory.

3.9 Pharmacovigilance. Within [***] of the Effective Date, the Parties shall negotiate and enter into a pharmacovigilance and safety agreement regarding Licensed Product consistent with industry practices (the "Pharmacovigilance & Safety Agreement") including: (a) providing detailed procedures regarding the maintenance of core safety information and the exchange of safety data relating to the Licensed Product within and outside the RareStone Territory within appropriate time frames and in an appropriate format to enable each Party to meet its expedited and periodic regulatory reporting requirements; and (b) ensuring compliance with the reporting requirements of all applicable Regulatory Authorities and all applicable legal and regulatory requirements for the management of safety data. The Pharmacovigilance & Safety Agreement shall provide for an adverse event database to collect adverse event and complaint information of the Licensed Products in the RareStone Territory to be maintained by RareStone [***] and procedures to facilitate the consolidation of information in the global safety database maintained by Rhythm and to prepare reports for Regulatory Authorities.

4. Supply of Licensed Product.

4.1 Supply Obligation. Rhythm shall be responsible for supplying Licensed Product to RareStone to allow RareStone to conduct its Development and Commercialization activities in the RareStone Territory under this Agreement, as the Parties shall agree to in separate supply agreements. Such supply shall either come from Rhythm, its Affiliates, or any of Rhythm's contract manufacturers of Licensed Product (each a "CMO"). No later than [***] prior to the anticipated commencement of Clinical Studies to be conducted by RareStone with respect to the Licensed Product, the Parties will negotiate and agree in good faith the terms of a full, separate manufacturing and supply agreement, covering supplies of Product for the Clinical Studies in the Territory (the "Clinical Supply Agreement"). No later than [***] prior to the anticipated date of obtaining Registration for the Licensed Product in the RareStone Territory of the Licensed Product, the Parties will enter into a new manufacturing and supply agreement, covering ordering and supplies for Commercialization activities in the RareStone Territory (the

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"Commercial Supply Agreement"). The Clinical Supply Agreement and Commercial Supply Agreement shall provide specific terms and obligations concerning, among other things, forecasts, purchase orders, and supply of Licensed Product for the RareStone Territory.

4.2 The transfer price [***] for Licensed Products by Rhythm will equal Rhythm's Manufacturing Cost, and RareStone shall have the right to audit Rhythm's books and records to verify the transfer price. The applicable supply agreements will include supply for all of RareStone's clinical and commercial requirements for Licensed Product prior to the receipt of the first approval by NMPA of the Licensed Product. Following the receipt of the first approval by NMPA, RareStone shall have the right to assume the license and rights to Manufacture Drug Product (but not the API or Drug Substance) for the Licensed Product, as further detailed in Section 4.4. In the event a Supply Failure, as defined in the applicable supply agreement, regarding the Licensed Product, RareStone shall have the right to assume the license and rights to Manufacture both the Drug Product and Drug Substance for the Licensed Product, as more fully detailed in the applicable supply agreement.

4.3 Quality Agreement. Together with the Clinical Supply Agreement, RareStone and Rhythm shall negotiate (or Rhythm shall use reasonable efforts to cause its applicable CMO to negotiate) and enter into a commercially reasonable and customary quality agreement related to the supply of Licensed Product (or component thereof) within [***] after the Effective Date.

4.4 Manufacturing Technology Transfer.

4.4.1 Notwithstanding anything to the contrary in this Agreement, from and after the date that is [***] after RareStone obtains Registration for the Licensed Product in the Territory, RareStone shall be entitled to request and receive from Rhythm all (or a copy of all, as applicable) Licensed Know-How that is reasonably necessary or useful for the Manufacture of Drug Product (but not the Manufacture of API or Drug Substance) for the Licensed Product, including, for clarity, the then-current process for the Manufacture of such Drug Product, as well as any improvements or enhancements to such processes, but excluding any Manufacturing processes, activities, or steps for Manufacture of API or Drug Substance (the "Manufacturing Process"), and Rhythm shall provide such support as may be necessary or reasonably useful to RareStone or its designee to use and practice the Manufacturing Process in the RareStone Territory, including by assisting RareStone or its designee to enter into agreements with any or all of Rhythm's CMOs and by waiving any exclusive arrangements Rhythm may have with such CMO in the RareStone Territory with respect to Licensed Compound and/or Licensed Product. Rhythm shall provide all such Licensed Know-How in such time and in such manner as reasonably agreed by the Parties.

4.4.2 Within [***] following a request to transition Drug Product Manufacturing, Rhythm shall develop and provide to RareStone a high-level plan describing the steps to be carried out in connection with the transfer of the Manufacturing Process set forth in Section 4.4.1 (the "Technology Transfer"). The Parties shall then cooperate to complete, within [***] of the delivery of such plan, the preparation of a reasonable implementation plan for a

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Technology Transfer, with such plan to include (a) specific timelines and milestones that are consistent with completion of the Technology Transfer within [***] (exclusive of any lead time for delivery to RareStone of any equipment of the type used by Rhythm or its CMO to Manufacture the Licensed Product) of RareStone's request, if any, for a Technology Transfer, and (b) a list of all equipment used by Rhythm or its CMO to Manufacture the Licensed Product, including a description of Rhythm's source (i.e., whether internally developed or procured from a Third Party) for each piece of such equipment. The Parties shall memorialize such implementation plan in a writing that is acknowledged by each Party.

5. Commercialization.

5.1 Exclusive Supply to RareStone. Rhythm, whether by itself or through an Affiliate or (sub)licensee, shall not, market, solicit orders for, sell, offer for sale, import, distribute, Commercialize or otherwise provide Licensed Product (a) to any Person in the RareStone Territory other than to RareStone or its designee or (b) to any Third Party if Rhythm, its relevant Affiliate or a (sub)licensee knows, or has reason to know, that Licensed Products sold or provided to such Third Party will be sold or transferred, directly or indirectly, for use in the RareStone Territory. Rhythm shall not enter into any agreement with any Person that would conflict or interfere with the foregoing obligation.

5.2 RareStone Obligation. RareStone shall use Commercially Reasonable Efforts (whether alone or with or through its Sublicensees and its or their respective Affiliates) to Commercialize the Licensed Product in the RareStone Territory, including without limitation for each indication for which Rhythm is eligible to receive milestone payments pursuant to Sections 7.3, [***].

5.3 Manner of Performance. RareStone will perform its Commercialization obligations under this Agreement in good scientific manner and in compliance with all applicable Laws.

5.4 Commercialization Plan.

5.4.1 Within [***] after the date that is [***] before RareStone's anticipated date of Registration in the RareStone Territory, RareStone shall prepare a reasonably detailed plan, including the timing of key activities, for the Commercialization of the Licensed Product in the Field in the RareStone Territory (the "Commercialization Plan"), and the Commercialization Plan will be automatically added to Exhibit E to this Agreement. From time to time, Rhythm will, through the JSC, provide RareStone with its then-current strategy and high-level plan for Commercialization of the Licensed Product outside the RareStone Territory; provided, that Rhythm shall not be obligated to create any documentation in order to comply with this Section 5.4.1.

5.4.2 RareStone shall provide the Commercialization Plan and Rhythm shall provide the information described in Section 5.4.1 to the JSC for its review, but, for clarity, neither Party shall be required to receive the JSC's approval of the Commercialization Plan or

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the information provided by Rhythm pursuant to Section 5.4.1, as applicable. RareStone shall prepare for the JSC's review updates of the Commercialization Plan (as defined in Section 6.1.2(b)) for each year until [***], and in any event, the JSC shall review the then-current Commercialization Plan in [***] (or more frequently as needed to address any material issues arising during such time period). For clarity, RareStone shall not be required to obtain the JSC's approval of any updates or amendments to the Commercialization Plan, although the JSC shall discuss any such updates or amendments in advance of their approval, and RareStone shall consider in good faith Rhythm's comments thereon.

5.5 Pricing and Reimbursement. Subject to any determination by applicable Regulatory Authorities, the pricing of the Licensed Products in the RareStone Territory shall be determined in accordance with Section 6.1. RareStone shall solely be responsible for obtaining any pricing or reimbursement approvals for the Licensed Product in the RareStone Territory as required by the applicable Regulatory Authority.

5.6 Sales and Marketing. RareStone shall be solely responsible, [***] for all Commercialization activities, including but not limited to training, compliance, promotion, marketing and medical affair activities, related to the Licensed Product in the RareStone Territory. All promotion activities related to the Licensed Product in the RareStone Territory shall be consistent with the Commercialization Plan and shall comply with all applicable Law. RareStone shall coordinate with Rhythm regarding medical affairs activities to ensure global coordination of medical affairs activities and priorities.

5.7 Marketing Materials. Visual aids, advertisements and promotional leaflets (the "Marketing Materials") concerning the Licensed Product for use in the RareStone Territory, as well as training manuals and education and communication materials (the "Educational Materials") for sales representatives in the RareStone Territory shall be developed and prepared by RareStone [***]. Any Marketing Materials, training manuals and/or Educational Materials developed and used by RareStone, its Affiliates and Sublicensees for the Licensed Product in the RareStone Territory shall be consistent with the Registration therein and the Commercialization Plan and shall comply with all applicable Laws. RareStone shall keep Rhythm reasonably informed with respect to Marketing Materials and Educational Materials and shall provide to Rhythm copies (in electronic form) of any new Marketing Materials and/or Educational Materials for the Licensed Product developed by RareStone (and/or any of its Affiliates or Sublicensees) and any material changes to any such Marketing Materials and/or Educational Materials, and consider in good faith Rhythm's reasonable comments, including with respect to the compliance with Rhythm's worldwide Licensed Product profile and this Section 5.5. Each Party shall have the right to use any Marketing Materials and Educational Materials developed by the other Party for Commercialization of the Licensed Product in the Field in its own territory.

5.8 Data Protection Laws. The Parties shall comply with all data protection laws with respect to the collection, use, storage, processing sharing, transfer and disclosure of personal identifiable data or information, in each case applicable to such Party's activities hereunder.

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5.9 Diversion. Each Party hereby covenants and agrees that it and its Affiliates shall not, and it shall contractually obligate (and use Commercially Reasonable Efforts to enforce such contractual obligation) its licensees, sublicensees and contractors not to, directly or indirectly, actively promote, market, distribute, import, sell or have sold any Licensed Product, including via the Internet or mail order, to any Third Party or to any address or Internet Protocol address or the like in the other Party's territory. Neither Party shall engage, nor permit its Affiliates, sublicensees or contractors to engage, in any advertising or promotional activities relating to any Licensed Product for use directed primarily to customers or other buyers or users of such product located in any country, Region or jurisdiction in the other Party's territory, or solicit orders from any prospective purchaser located in any country, Region or jurisdiction in the other Party's territory.

6. Governance.

6.1 Joint Steering Committee.

6.1.1 Establishment. Within [***] following the Effective Date, Rhythm and RareStone shall establish a JSC to facilitate the exchange of information, including clinical, regulatory, medical, pharmacovigilance, manufacturing, and commercial matters related to the Licensed Product, in the RareStone Territory, subject to the provisions of this Section 6.1.

6.1.2 Duties. The JSC shall:

(a) Facilitate communications and discussion between the Parties with respect to the Licensed Product;

(b) Review, discuss and coordinate the overall strategy and activities for the Registration, Manufacturing, and Commercialization of Licensed Products in the RareStone Territory, including related regulatory activities;

(c) Review and discuss the Commercialization Plan and any substantive amendments, updates and other modifications thereto from time to time as provided for in this Agreement;

(d) Provide a forum for resolving matters referred to the JSC pursuant to the procedures set out in Section 6.1.5 below;

(e) Oversee the activities of the JDC and attempt to resolve issues presented to it by and disputes within the JDC; and

(f) Perform such other duties and responsibilities as are specifically assigned to the JSC by mutual written agreement of the Parties, except where in conflict with any provision of this Agreement.

6.1.3 Membership. The JSC shall be composed of an equal number of representatives from each of RareStone and Rhythm, selected by such Party. Unless the Parties otherwise mutually agree, the exact number of representatives for each of RareStone and Rhythm

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shall be, with respect to the JSC, [***]. Either Party may replace its respective JSC representatives at any time with prior written notice to the other Party; provided that the criteria for composition of the JSC set forth in the preceding sentence continues to be satisfied following any such replacement of a Party's representative on the JSC.

6.1.4 Meetings. The JSC shall meet at least twice each year, or at such other intervals as agreed to by the Parties or more frequently as necessary to resolve any issues submitted for JSC resolution by the JDC. All JSC meetings may be conducted by telephone, video-conference or in person as determined by the JSC. [***]. With the consent of the Parties (not to be withheld unreasonably), other appropriate employee representatives of the Parties may attend the JSC meeting as non-voting observers, provided that such observers are subject to obligations of confidentiality substantially similar to the provision set forth in Article 9.

6.1.5 Decision-Making.

(a) Decisions of the JSC shall be made by unanimous vote, with [***] representative from each Party participating in any vote.

(b) In the event that the JSC does not reach consensus with respect to a particular matter within [***] after the matter is submitted to the JSC, then either Party may, by written notice to the other Party, have such matter referred to (i) Rhythm's Chief Executive Officer on the part of Rhythm and (ii) RareStone's Chief Executive Officer on the part of RareStone (collectively, "Senior Executives") who shall meet promptly and negotiate in good faith to attempt to resolve the dispute.

(c) If, despite such good faith efforts, the Senior Executives are unable to resolve such dispute during such meeting, then RareStone shall have the right to cast the deciding vote with respect to any such matter; provided, that if such matter is with respect to the Development of the Licensed Product in the RareStone Territory and would reasonably be likely to result in a material adverse risk to the Development or Commercialization of the Licensed Product in the Rhythm Territory (as determined at Rhythm's reasonable discretion), Rhythm will have a veto right over such decision.

(d) For clarity, neither Party shall have the right to cast a deciding vote to excuse itself from any of its obligations specifically enumerated under this Agreement.

(e) For additional clarity, the Senior Executive of RareStone will have final decision-making authority with respect to any decisions solely related to Commercialization of the Licensed Product in the RareStone Territory (including pricing).

6.2 Joint Development Committee.

6.2.1 Establishment. Within [***] following the Effective Date, Rhythm and RareStone shall establish a JDC to facilitate the Development and regulatory activities

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related to the Licensed Product, in the RareStone Territory, subject to the provisions of this Section 6.2.

6.2.2 Duties. The JDC shall:

(a) Review, discuss, and approve the Clinical Development Plan, including any substantive amendments, updates and other modifications thereto, and oversee its implementation.

(b) Review and discuss the regulatory strategy and any substantive amendments, updates and other modifications thereto from time to time as provided for in this Agreement and oversee its implementation;

(c) Provide periodic reports to the JSC regarding the Clinical Development Plan and Regulatory Plan; and

(d) Perform such other duties and responsibilities as are specifically assigned to the JDC by the JSC, except where in conflict with any provision of this Agreement.

6.2.3 Membership. The JDC shall be composed of an equal number of representatives from each of RareStone and Rhythm, selected by such Party. Unless the Parties otherwise agree, the exact number of representatives for each of RareStone and Rhythm shall be, with respect to the JDC, [***] representatives. Either Party may replace its respective JDC representatives at any time with prior written notice to the other Party; provided that the criteria for composition of the JDC set forth in the preceding sentence continues to be satisfied following any such replacement of a Party's representative on the JDC.

6.2.4 Meetings. The JDC shall meet at least once per month prior to [***] of the Effective Date and at least once per Calendar Quarter thereafter, or at such other intervals as agreed to by the JSC. All JDC meetings may be conducted by telephone, video-conference or in person as determined by the JDC. [***]. With the consent of the Parties (not to be withheld unreasonably), other appropriate employee representatives of the Parties may attend the JDC meeting as non-voting observers.

6.2.5 Decision-Making.

(a) Decisions of the JDC shall be made by unanimous vote, with [***] from each Party participating in any vote.

(b) In the event that the JDC does not reach consensus with respect to a particular matter within [***] after the matter is submitted to the JDC, then either Party may, by written notice to the other Party, have such matter referred to the JSC. Any particular matter referred to the JSC shall be subject to the decision-making process of the JSC as set forth in Section 6.1.5.

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(c) For clarity, neither Party shall have the right to cast a deciding vote to excuse itself from any of its obligations specifically enumerated under this Agreement.

6.3 Appointment of Alliance Managers. Promptly following the Effective Date, each Party shall appoint a person to act as its alliance manager to coordinate its business activities under this Agreement (each such person, an "Alliance Manager"). Each Party shall notify in writing the other Party as soon as practicable upon making, and changing, this appointment. The Alliance Managers shall be the primary business contacts under this Agreement and are charged with ensuring a collaborative alliance environment to ensure timely development and Commercialization of Licensed Product in the RareStone Territory. The Alliance Manager shall respond to all reasonable requests and other communications from the either Party and the JSC and shall address any other issues raised by the same regarding the management, exchange of information or conduct of the activities of the Parties under this Agreement.

6.4 Scope of Governance. Notwithstanding the creation of the JSC and the JDC, each Party shall retain the rights, powers and discretion granted to it under this Agreement, and the JSC or the JDC shall not be delegated or vested with rights, powers or discretion unless such delegation or vesting is expressly provided herein, or the Parties expressly so agree in writing. The JSC and the JDC shall not have the power to amend or modify this Agreement, and no decision of the JSC or JDC shall be in contravention of any terms and conditions of this Agreement. The Alliance Managers shall not have any rights, powers or discretion, except as expressly granted to the Alliance Managers under this Agreement and in no event shall the Alliance Managers have any power to modify or amend this Agreement. It is understood and agreed that issues to be formally decided by the JSC and JDC are only those specific issues that are expressly provided in this Agreement to be decided by the JSC and JDC. It is also understood that the JSC and JDC shall not have any authority over activities related to the Development and/or Commercialization of the Licensed Product for use in the Rhythm Territory.

7. Financial Terms.

7.1 Upfront Payment. Within [***] after the Effective Date, RareStone shall pay to Rhythm an upfront fee of Seven Million ($7,000,000) USD in accordance with the payment provisions of Section 7.8.

7.2 Upfront Equity Issuance. RareStone shall issue to Rhythm a total of (#) ordinary shares of equity, subject to a equity issuance agreement in the form attached hereto as Exhibit F ("Equity Agreement") within [***] after the Effective Date ("Initial Equity Shares"). RareStone represents to Rhythm that, as of the Effective Date, the Initial Equity Shares are equivalent to Five Million ($5,000,000) USD.

7.3 NMPA Milestone Payments. Within [***] calendar days following the first achievement of each of the following milestone events, RareStone shall give written notice thereof to Rhythm and shall pay to Rhythm the corresponding one-time, non-creditable, non-refundable milestone payments:

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Milestone Event	Milestone Payment
[NMPA granting the Obesity due to suspected Biallelic POMC-, PCSK1-, or LEPR-deficiency clinical trial waiver for the Licensed Product in mainland China]	[Five Hundred Thousand ($500,000) USD]
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]

For the avoidance of doubt, under no circumstance shall RareStone be obligated to pay Rhythm more than an aggregate [***] for regulatory approval by the NMPA, regardless of future gene approval indications.

7.4 FDA Milestone Payments. Within [***] following the first achievement of each of the following milestone events, Rhythm shall give written notice thereof to RareStone, and RareStone shall pay to Rhythm the corresponding one-time, non-creditable, non-refundable milestone payments:

Milestone Event	Milestone Payment
[FDA approval of Licensed Product in the U.S. for Heterozygous PMOC or PSCK1]	[Five Hundred Thousand ($500,000) USD]
[***]	[***]
[***]	[***]
[***]	[***]

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Milestone Event	Milestone Payment
[***]	[***]
[***]	[***]

For the avoidance of doubt, under no circumstance shall RareStone be obligated to pay Rhythm more than an aggregate [***] for regulatory approval by the FDA, regardless of future gene approval indications.

7.5 Sales Milestone Payments. Within [***] following the end of the calendar year in which each of the following milestone events is first achieved, RareStone shall give written notice thereof to Rhythm and shall pay to Rhythm the corresponding one-time, non-creditable, non-refundable milestone payments:

Milestone Event	Milestone Payment
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]

7.6 Royalties.

7.6.1 Subject to the terms and conditions of this Agreement, RareStone shall pay to Rhythm, on a quarterly basis, royalties equal to the following percentage of Net Sales of the Licensed Product during the applicable Payment Period, as calculated by multiplying the applicable sales royalty rate by the corresponding amount of incremental Net Sales in the RareStone Territory ("Royalties"), as follows:

Aggregate Annual Net Sales	Sales Royalty Rate
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]

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7.6.2 If RareStone, its Sublicensees or its or their respective Affiliates is required to pay royalties to any Third Party in order to make, have made, use, sell, offer to sale or import Licensed Product, then RareStone shall have the right to credit [***] of such Third Party royalty payments against the Royalties owing to Rhythm under this Section 7.6, provided however that such Royalties shall not be reduced by more than [***] by reason of this Section 7.6.2.

7.6.3 On a Region-by-Region basis, upon the launch of the first (1st) Generic Product in such Region, the applicable Royalties under this Section 7.6 for Licensed Product in such Region shall be reduced by [***].

7.6.4 Notwithstanding the foregoing, during any calendar quarter in the Payment Period for the Licensed Product in a Region in the RareStone Territory, the operation of Section 7.6.2 and Section 7.6.3, individually or in combination, shall not reduce the final royalty rate to less than [***] of the royalty rate that would have applied pursuant to Section 7.6.1 prior to any reduction, in each case, in such Region during such calendar quarter.

7.7 Royalty Reports and Payments. Within [***] after the end of each calendar quarter during the term of this Agreement, commencing with the calendar quarter in which the First Commercial Sale occurs, RareStone shall deliver to Rhythm a report setting forth its good faith estimates for such calendar quarter regarding the following information: (a) the calculation of applicable royalties, if any, which shall have accrued based upon sales in such calendar quarter; (b) the applicable withholding taxes, if any, required by law to be deducted with respect to such sales; and (c) the applicable exchange rate, if any, as determined below. Within [***] after the end of after the end of each calendar quarter during the term of this Agreement, commencing with the calendar quarter in which the First Commercial Sale occurs, RareStone shall deliver to Rhythm an update to such estimate reflecting the final information set forth in (a) through (c). No such reports or payments shall be due prior to the First Commercial Sale of the Licensed Product. With respect to Net Sales received in a currency other than United States dollars, all amounts shall be expressed both in the currency in which the amount is invoiced (or received as applicable) and in the United States dollar equivalent. The United States dollar equivalent shall be calculated using the average of the exchange rate (local currency per US$1) which corresponds to the rate for such currency reported in The Wall Street Journal, Internet U.S. Edition at www.wsj.com, as of the last Business Day of each calendar month within such calendar quarter.

7.8 Payment Provisions.

7.8.1 The Royalty shown to have accrued by each report of final information provided for under Section 7.7 shall be due on the date such report is due. Payment of the Royalty in whole or in part may be made in advance of such due date. If within [***] after the end of each calendar year RareStone identifies any amounts actually payable to Rhythm that have not been paid during such calendar year, RareStone shall make a reconciling payment to Rhythm as needed to give effect to the payments actually due to Rhythm for such calendar year.

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7.8.2 All payments by RareStone to Rhythm hereunder shall be in United States dollars. If at any time legal restrictions prevent the prompt remittance of part or all of a Royalty payment hereunder with respect to the RareStone Territory, RareStone shall have the right, in its sole discretion, to make such payments by depositing the amount thereof in local currency (or in another currency selected by Rhythm, if feasible) to Rhythm's account in a bank or other depository institution in the RareStone Territory. RareStone shall provide prompt written notice to Rhythm of such legal restrictions, and the Parties shall cooperate to transfer such locally-deposited amounts to Rhythm promptly after such legal restrictions are removed. Notwithstanding the foregoing, in the event that RareStone fails to make [***] consecutive Royalty payments on time and in United States dollars due to such a legal restriction, Rhythm shall have the right to suspend RareStone's Commercialization rights with respect to Licensed Products under this Agreement until such time as such legal restriction no longer prevents the prompt remittance of part or all of a Royalty payment hereunder with respect to the RareStone Territory.

7.8.3 Any payments or portions thereof due under this Agreement that are not paid by the date such payments are due under this Agreement or that have been deposited to a local account pursuant to Section 7.8.2 shall bear interest at a rate equal to [***]. This Section 7.8.3 shall in no way limit any other remedies available to the Parties.

7.8.4 Unless otherwise expressly stated in this Agreement, all amounts specified in this Agreement are in United States dollars, and all payments by one Party to the other Party under this Agreement shall be paid in United States Dollars. If any currency conversion shall be required in connection with the payment of Royalties or other amounts under this Agreement, such conversion shall be calculated in accordance with Section 7.7.

7.9 Taxes

7.9.1 Withholding Taxes. Payments made by RareStone to Rhythm pursuant to this Agreement shall not be reduced on account of any taxes. For clarity, milestone and Royalty payments will be made at the fully-stated amounts. In the event that RareStone assigns or otherwise transfers its rights or obligations under this Agreement to one of its Affiliates that is not resident for tax purposes in the Cayman Islands, or, after the Effective Date, changes its tax residence or the permanent establishment to which the rights under this Agreement are allocated, RareStone shall be responsible for such incremental tax withholding.

7.9.2 Sales Taxes. Any sales taxes (including any consumption tax or value added tax), use tax, transfer taxes, duties or similar governmental charges required to be paid in connection with any payments by RareStone to Rhythm hereunder shall be as required by the applicable Law. In the event that Rhythm is required to pay any such amounts, RareStone shall promptly remit payment to Rhythm of such amounts.

7.10 Records; Audits. RareStone shall keep, and require its Affiliates and Sublicensees to keep, complete, true and accurate books of accounts and records for the purpose of determining the amounts payable to Rhythm pursuant to this Agreement. Such books and

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records shall be kept for [***] following the end of each calendar year to which they pertain. Upon the written request of Rhythm and not more than once in each calendar year, RareStone shall permit an independent certified public accounting firm of nationally recognized standing selected by Rhythm and reasonably acceptable to RareStone [***], to have access during normal business hours to such of the financial records of RareStone, its Affiliates and Sublicensees, as may be reasonably necessary to verify the accuracy of the royalty reports hereunder for the [***] immediately prior to the date of such request (other than records for which Rhythm has already conducted an audit under this Section). If such accounting firm concludes that additional amounts were owed during the audited period, RareStone shall pay such additional amounts within [***] after the date Rhythm delivers to RareStone such accounting firm's written report so concluding, together with interest on such unpaid amounts at the rate set forth in Section 7.8.3 above. The fees charged by such accounting firm shall be paid by Rhythm; provided, however, if the audit discloses a variation or error producing an underpayment in amounts payable exceeding [***] of the amount paid for a period covered by the audit is established, in which case RareStone shall pay all reasonable fees and expenses charged by such accounting firm for conducting the audit. Rhythm shall cause its accounting firm to retain all financial information subject to review under this Section 7.10 in strict confidence; provided, however, that RareStone shall have the right to require that such accounting firm, prior to conducting such audit, enter into an appropriate non-disclosure agreement with RareStone regarding such financial information. Rhythm shall treat all such financial information as RareStone's confidential information, and shall not disclose such financial information to any Third Party or use it for any purpose other than as specified in this Section 7.10. Additionally, RareStone will allow the counterparties to the Upstream Agreements to conduct audit rights to the extent such counterparties have rights to conduct audits of sublicensees under the Upstream Agreements.

8. Indemnification.

8.1 Indemnification of RareStone by Rhythm. Subject to the provisions of this Section 8, Rhythm shall indemnify, defend and hold harmless RareStone, its Affiliates, and its and their respective officers, directors, agents, and representatives (the "RareStone Indemnitees"), from and against any and all losses, liabilities, damages and expenses (including reasonable attorneys' fees and costs) (collectively, "Losses") incurred by any RareStone Indemnitee resulting from any claim, demand, action or proceeding brought by any Third Party (each a "Claim") to the extent resulting from or arising out of:

8.1.1 the Development, use or Commercialization of the Licensed Product by or on behalf of Rhythm, its licensee(s) for the Rhythm Territory, or their respective Affiliates, customers or end users;

8.1.2 the breach of any representations, warranties or covenants of Rhythm in this Agreement; or

8.1.3 the negligence, gross negligence or willful misconduct of Rhythm, its Affiliates or their respective agents or representatives in performing Rhythm's obligations or exercising Rhythm's rights under this Agreement.

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8.2 Indemnification of Rhythm by RareStone. Subject to the provisions of this Section 8, RareStone shall indemnify and hold harmless Rhythm, its Affiliates, and its and their respective officers, directors, agents, and representatives (the "Rhythm Indemnitees"), from and against any and all Losses incurred by any Rhythm Indemnitee resulting from any Claim to the extent resulting from or arising out of:

8.2.1 the Development, use or Commercialization of Licensed Product by or on behalf of RareStone, its Sublicensee(s) for the RareStone Territory, or their respective Affiliates, customers or end users, including any activities carried out by or on behalf of RareStone in its capacity as Rhythm's regulatory agent pursuant to Section 3.2, and except to the extent arising out of (a) the non-compliance by Rhythm of product specifications set forth in the Supply Agreement or the Current Good Manufacturing Practice Regulations enforced by the FDA ("cGMPs"); or (b) the actual or alleged infringement, misappropriation or other violation of any intellectual property rights of a Third Party by the Licensed Product or use thereof or the use of the Licensed Marks in accordance with this Agreement;

8.2.2 the breach of any representations, warranties or covenants of RareStone in this Agreement; or

8.2.3 the negligence, gross negligence or willful misconduct of RareStone, its Affiliates or their respective agents or representatives in performing RareStone's obligations or exercising RareStone's rights under this Agreement.

8.3 Procedure. A Party seeking indemnification (the "Indemnitee") shall promptly notify the other Party (the "Indemnifying Party") in writing of a Claim; provided that an Indemnitee's failure to give such notice or delay in giving such notice shall not affect such Indemnitee's right to indemnification under this Section 8 except to the extent that the Indemnifying Party has been prejudiced by such failure or delay. The Indemnifying Party shall have the right to control the defense of all indemnification Claims hereunder. The Indemnitee shall have the right to participate [***] in the Claim with counsel of its own choosing. The Indemnifying Party shall consult with the Indemnitee in good faith with respect to all non-privileged aspects of the defense strategy. The Indemnitee shall cooperate with the Indemnifying Party as reasonably requested, [***]. The Indemnifying Party shall not settle any Claim without the Indemnitee's prior written consent, which consent shall not be unreasonably withheld, conditioned or delayed.

8.4 No Consequential Damages. NOTWITHSTANDING ANYTHING TO THE CONTRARY HEREIN, EXCEPT WITH RESPECT TO A BREACH OF SECTION 9 OR WITH RESPECT TO A PARTY'S OBLIGATIONS TO INDEMNIFY, DEFEND AND HOLD HARMLESS PURSUANT TO SECTION 8, NEITHER PARTY SHALL BE LIABLE FOR ANY SPECIAL, INDIRECT, INCIDENTAL OR CONSEQUENTIAL DAMAGES, WHETHER FORESEEABLE OR NOT, WHETHER IN CONTRACT, WARRANTY, TORT, NEGLIGENCE OR OTHERWISE, ARISING OUT OF THIS AGREEMENT OR THE EXERCISE OF ITS RIGHTS HEREUNDER, REGARDLESS OF ANY NOTICE OF SUCH DAMAGES.

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9. Confidentiality.

9.1 Confidential Information. During the Term of this Agreement, and for a period of [***] following the expiration or earlier termination hereof, each Party shall maintain in confidence all information of the other Party that is disclosed by the other Party and identified as, or acknowledged to be, or that is by nature would reasonably be deemed, confidential at the time of disclosure (the "Confidential Information"), and shall not use, disclose or grant the use of the Confidential Information, except on a need-to-know basis to (a) those directors, officers, Affiliates, employees, licensees and sublicensees (with respect to Rhythm), permitted Sublicensees (with respect to RareStone), permitted actual or prospective assignees and agents, consultants, clinical investigators or contractors, to the extent such disclosure is reasonably necessary in connection with performing its obligations or exercising its rights under this Agreement or complying with applicable Laws. For purposes of this Section 9.1, the Licensed Product and all uses thereof shall constitute the Confidential Information of both Parties. To the extent that disclosure is authorized by this Agreement, prior to disclosure, the disclosing Party shall enter into a (or have already entered into an existing) written confidentiality agreement with any such Person as materially protective of such Confidential Information and the disclosing Party as this Section 9. Each Party shall notify the other promptly upon discovery of any unauthorized use or disclosure of the other Party's Confidential Information.

9.2 Terms of this Agreement. Except as otherwise provided in this Section 9, neither Party shall disclose any terms or conditions of this Agreement to any Third Party without the prior consent of the other Party; provided, however, that a Party may disclose the terms or conditions of this Agreement, (a) on a need-to-know basis to its legal and financial advisors to the extent such disclosure is reasonably necessary, (b) to a Third Party in connection with (i) an equity investment in or financing of such Party, (ii) a merger, consolidation or similar transaction by such Party, (iii)(A) with respect to Rhythm, an actual or potential licensee or sublicensee and (B) with respect to RareStone, an actual or bona fide prospective permitted Sublicensee, or (iv) the sale of all or substantially all of the assets of such Party, on a need to know basis, and in each case under appropriate confidentiality provisions substantially equivalent to those in this Agreement.

9.3 Permitted Disclosures. The confidentiality obligations contained in this Section 9 shall not apply to the extent that (a) a Party is required (i) to disclose Confidential Information or the terms of this Agreement by applicable Law, regulation, rule (including rule of a stock exchange or automated quotation system), order of a Governmental Authority or a court of competent jurisdiction or legal process, including tax authorities, or (ii) to disclose information to any Regulatory Authority for purposes of obtaining approval to test or market the Licensed Product, provided in either case that, to the extent practicable, such Party shall provide written notice thereof to the other Party and sufficient opportunity to object to or petition to limit any such disclosure or to request confidential treatment thereof; or (b) a Party can demonstrate that the Confidential Information (i) was public knowledge at the time of its disclosure or became public knowledge after its disclosure, other than as a result of actions of such Party in violation hereof; (ii) was already known to the receiving Party, other than under an obligation of confidentiality, at the time of disclosure; (iii) was developed by the receiving Party without use

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of or reference to any Confidential Information of the disclosing Party or (iv) was disclosed to the receiving Party on an unrestricted basis from a source unrelated to any Party to this Agreement and not under a duty of confidentiality to the disclosing Party.

9.4 Injunctive Relief. Each Party acknowledges that it will be impossible to measure in money the damage to the other Party if such Party fails to comply with the obligations imposed by this Section 9, and that, in the event of any such failure, the other Party may not have an adequate remedy at law or in damages. Accordingly, each Party agrees that injunctive relief or other equitable remedy, in addition to remedies at law or damages, is an appropriate remedy for any such failure and shall not oppose the granting of such relief on the basis that the disclosing Party has an adequate remedy at law. Each Party agrees that it shall not seek, and agrees to waive any requirement for, the securing or posting of a bond in connection with the other Party seeking or obtaining such equitable relief.

9.5 Publication of Clinical Data. Prior to publishing, publicly presenting and/or submitting for written or oral publication a manuscript, abstract or the like that includes Data from Clinical Studies with respect to the Licensed Product that has not previously published pursuant to this Section 9.5, RareStone shall provide Rhythm a copy thereof for its review and approval for [***] (unless RareStone is required by Law or regulation, including the rules of any applicable securities exchange, to publish such information sooner). RareStone shall consider in good faith and integrate into such publication any reasonable comments provided by Rhythm during such [***] period. In addition, RareStone shall, at the request of Rhythm, remove any Confidential Information of Rhythm therefrom, except RareStone shall have the right to publicly disclose any information, including Confidential Information, pertaining to safety of the Licensed Product that RareStone believes in good faith it is obligated or appropriate to disclose under applicable Law or applicable medical ethical guidelines.

9.6 Press Releases. The Parties have agreed to a press release to be made on or after the Effective Date, set forth in Exhibit G. No Party will release any other press release relating to the Licensed Product in the RareStone Territory without the prior written approval of the other Party.

9.7 Prior Non-Disclosure Agreements. Upon execution of this Agreement, the terms of this Section 9 shall supersede any prior non-disclosure, secrecy, or confidentiality agreement between the Parties, including the confidentiality agreement effective between the Parties dated [***] and any amendment thereto. Any information disclosed under such prior agreements shall be deemed disclosed under this Agreement.

10. Intellectual Property Rights.

10.1 Ownership of Inventions.

10.1.1 Inventorship of inventions, improvements, developments or discoveries, whether patentable or non-patentable, invented or otherwise developed or generated by either Party or its Affiliates, or any of its or their employees, sublicensees (where permitted),

independent contractors or agents during the Term, in the course of Developing, Manufacturing or Commercializing any Licensed Product under this Agreement ("Inventions"), and any and all intellectual property rights therein, will be determined based on the principles of inventorship in accordance with United States patent Laws.

10.1.2 Any Invention made, conceived, reduced to practice, or otherwise discovered solely by the employees, independent contractors, or agents of Rhythm ("Rhythm Inventions"), and all intellectual property rights therein, will be solely owned by Rhythm. Any Invention made, conceived, reduced to practice, or otherwise discovered jointly by the employees, independent contractors, or agents of Rhythm and RareStone ("Joint Inventions"), and all intellectual property rights therein, will be solely owned by Rhythm. All Rhythm Inventions and Joint Inventions, and any intellectual property rights therein, including any Patents disclosing such Rhythm Inventions and Joint Inventions, shall be automatically included in the Licensed Technology and Registered IP Rights, and shall be licensed to RareStone pursuant to Section 2.1.1. Subject to the terms and conditions of this Agreement, Rhythm hereby grants to RareStone an irrevocable, perpetual, royalty-free, fully-paid up, nonexclusive license under Rhythm's interest in the Joint Inventions to Develop, Manufacture, Commercialize and otherwise exploit products that are claimed or covered by the Joint Inventions. Any Invention made, conceived, reduced to practice, or otherwise discovered solely by the employees, independent contractors, or agents of RareStone ("RareStone Inventions"), and all intellectual property rights therein, will be solely owned by RareStone. RareStone shall disclose in writing to Rhythm all RareStone Inventions promptly following the generation, conception, reduction to practice or other discovery thereof. RareStone hereby grants to Rhythm an irrevocable, perpetual, royalty-free, fully-paid up, exclusive license, with the right to grant sublicenses, under RareStone Inventions in the Rhythm Territory solely for the Development, Manufacture and Commercialization of Licensed Products.

10.1.3 RareStone shall, and shall cause its Sublicensees and Affiliates, and all contractors, employees, and agents, to cooperate with Rhythm and take all reasonable actions and execute such agreements, declarations, assignments, legal instruments and documents as may be reasonably required to perfect Rhythm's right, title and interest in and to all Joint Inventions and all intellectual property rights therein. Each Party will cause all employees of such Party who perform activities for such Party under this Agreement to be under an obligation to assign their rights in any Inventions, whether or not patentable, resulting therefrom to such Party so such Inventions shall be owned in accordance with Section 10.1.2. With respect to any activities of a Party under this Agreement that are contracted to a Person that is not an employee, the Party retaining such contractor will use Commercially Reasonable Efforts to include in the applicable contract an assignment to such Party of all rights in Patent Rights and Know-How made by such contractor resulting from such activities, and in any event will include in the applicable contract a license to such Party that is sublicensable to the other Party under this Agreement, of any Patent Rights and Know-How made by such contractor resulting from such activities.

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10.2 Prosecution and Maintenance.

10.2.1 Except as otherwise set forth in Section 10.1, Rhythm shall have the sole right, [***], to prepare, file, prosecute and maintain the Registered IP Rights in the RareStone Territory. Rhythm shall consider in good faith the interests of RareStone in so doing. RareStone shall assist Rhythm, upon request and [***], and to the extent commercially reasonable, in connection therewith. Rhythm shall (a) provide RareStone with any Licensed Mark application and patent application within the Registered IP Rights filed by Rhythm reasonably in advance of filing and receive and consider in good faith reasonable comments by RareStone thereon; (b) provide RareStone with any such Licensed Mark application and patent application filed by Rhythm promptly after such filing; (c) provide RareStone with copies of all material correspondence and communications received regarding the Registered IP Rights and consider in good faith reasonable comments by RareStone in connection therewith; (d) provide RareStone with copies of all material correspondence and communications sent regarding the Registered IP Rights; and (e) notify RareStone of any interference, opposition, reexamination request, nullity proceeding, appeal or other similar action filed for any Registered IP Right, review it with RareStone as reasonably requested, and receive and consider in good faith reasonable comments by RareStone thereon.

10.2.2 Rhythm shall not abandon any Licensed Patent in the RareStone Territory without providing to RareStone written notice thereof reasonably in advance of any such abandonment. RareStone shall have the right to assume responsibility for prosecuting and maintaining such Licensed Patent by providing Rhythm written notice thereof within [***] after receipt of the notice to abandon, whereupon Rhythm shall assist RareStone, upon request and to the extent commercially reasonable, in connection with the continued prosecution and maintenance of such Licensed Patent, [***].

10.3 Enforcement and Defense.

10.3.1 Each Party shall promptly notify the other Party in writing of any actual or threatened infringement, violation or misappropriation known to such Party of any Registered IP Rights or Licensed Know-How in the RareStone Territory and shall provide the other Party with the available evidence, if any, of such infringement, violation or misappropriation.

RareStone shall have the first right, but not the obligation, to initiate proceedings or take other appropriate action in the RareStone Territory, [***], to enforce the Registered IP Rights against any Third Party or to prevent, cease, and/or remedy any misappropriation, improper disclosure, or other misuse of the Licensed Know-How by any Third Party (collectively, “Enforcement Proceeding(s)”). RareStone shall consider in good faith the interests of Rhythm in so doing. If RareStone does not initiate proceedings or take other appropriate action within [***] of receipt of a request by Rhythm to initiate an Enforcement Proceeding, then Rhythm shall be entitled to initiate Enforcement Proceedings or take other appropriate action against such Third Party, [***], and to include RareStone as a nominal party plaintiff. The Party conducting such Enforcement Proceeding shall have full control over its conduct, including settlement thereof;

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provided, however, that the Party conducting such action may not settle any such action, or make any admissions or assert any position in such Enforcement Proceeding (other than an assertion of Patents), in a manner that would materially adversely affect the rights or interests of the other Party, without the prior written consent of the other Party, which shall not be unreasonably withheld, conditioned or delayed. In any event, the Parties shall assist one another and cooperate in any such Enforcement Proceeding at the other's reasonable request.

10.3.2 With respect to any Enforcement Proceeding, all monies recovered upon the final judgment or settlement of any such Enforcement Proceeding shall be applied as follows: (a) first, to reimburse the costs and expenses (including reasonable attorneys' fees and costs) of RareStone and Rhythm; and (b) second, to the Party prosecuting such Enforcement Proceeding.

10.4 Third Party Infringement Claims. If the manufacture, sale or use of the Licensed Product in the RareStone Territory pursuant to this Agreement results in a claim, suit or proceeding alleging patent infringement against Rhythm or RareStone (or their respective Affiliates, licensees or Sublicensees) (collectively, "Infringement Actions"), such Party shall promptly notify the other Party hereto in writing. Neither Party shall settle such Infringement Action, or make any admissions or assert any position in such Infringement Action, in a manner that would adversely affect the Licensed Product, the manufacture, use or sale or Commercialization of the Licensed Product, or Rhythm's rights in the Licensed IP Rights, without the prior written consent of the other Party, which shall not be unreasonably withheld, conditioned or delayed.

10.5 Registration of License. RareStone shall have the right to register or record its license under the Registered IP Rights with the relevant Governmental Authorities in the RareStone Territory to the extent that such registration or recordation is reasonably necessary in order for RareStone to carry out its obligations under this Agreement. RareStone shall, [***], prepare and deliver to Rhythm such instruments and other documents reasonably necessary and in proper form for such registration. The Parties shall reasonably agree on the form of documents to be used for such purpose, and shall cooperate to preserve confidentiality of this Agreement to the extent permitted under applicable Laws in the RareStone Territory. Rhythm shall execute and return to RareStone such instruments and documents promptly after mutual agreement on the form and receipt thereof.

10.6 Upstream Agreements. The Parties acknowledge that in exercising their rights and performing their obligations under Sections 10.2 and 10.3, they will give effect to the rights of the counterparties to, and the obligations of Rhythm under, the Upstream Agreements with respect to prosecution, maintenance and enforcement of Registered IP Rights or Licensed Know-How in the RareStone Territory.

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11. Trademarks.

11.1 Display.

11.1.1 Pursuant to the license in Section 11.2, RareStone shall have the right to display the Licensed Marks, as listed in Exhibit B, on any and all packaging materials, labels and Marketing Materials for the Licensed Product shall display the Licensed Marks.

11.1.2 The Licensed Product shall be sold in the RareStone Territory under the trade name of RareStone, provided, however that to the extent permissible under applicable Law within the RareStone Territory, such packaging materials, labels and Marketing Materials shall also display the trade name of Rhythm in reasonable size and prominence, as reasonably approved by Rhythm. The trademarks of RareStone, trade dress, style of packaging and the like with respect to the Licensed Product in the RareStone Territory may be determined by RareStone in a manner that is consistent with RareStone's standard trade dress and style.

11.2 Grant of License. Rhythm hereby grants to RareStone an exclusive license to use the Licensed Marks and Rhythm's trade name in the RareStone Territory in the Commercialization of the Licensed Product in accordance with this Agreement (the "Trademark License"). The ownership and all goodwill from the use of the Licensed Marks and Rhythm's trade name shall vest in and inure to the exclusive benefit of Rhythm.

11.3 Registration of Trademarks. Rhythm (or its designee) shall be responsible for filing and registering [***] in its own name (to the extent permitted by applicable Law), appropriate registrations for such Licensed Marks in the RareStone Territory.

11.4 Approval of Packaging and Promotional Materials. Without limiting Section 5.5 above, to preserve Rhythm's legal rights in the Licensed Marks, RareStone shall submit representative Marketing Materials, packaging and Licensed Product displaying the Licensed Marks and/or Rhythm's trade name to Rhythm for Rhythm's review and approval, not to be unreasonably withheld, conditioned or delayed, prior to the first use of such Marketing Materials, packaging or Licensed Product and prior to any subsequent change or addition to such Marketing Materials, packaging or Licensed Product; provided that if Rhythm has not responded within [***] after the submission of such Marketing Materials, packaging or Licensed Product, Rhythm's approval will be deemed to have been received.

11.5 Termination of Trademark License. RareStone's right to use the Licensed Marks and the Rhythm trade name shall terminate in the RareStone Territory upon termination or expiration of the Trademark License. RareStone shall take all such steps as Rhythm may reasonably request to give effect to the termination of the license to the Licensed Marks and Rhythm trade name in the RareStone Territory and to record any documents that may be required to evidence the termination of such license and transfer to Rhythm of all rights, registrations, recordations and the like for such Licensed Marks.

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11.6 Domain Names. The Parties shall discuss in good faith and agree upon how to handle domain names containing the Licensed Marks.

12. Representations and Warranties.

12.1 Mutual Representations and Warranties. Each Party represents and warrants to the other Party as follows:

12.1.1 Such Party is duly organized, validly existing and in good standing under the laws of the jurisdiction in which it is organized.

12.1.2 Such Party (a) has the requisite power and authority and the legal right to enter into this Agreement and to perform its obligations hereunder; and (b) has taken all requisite action on its part to authorize the execution and delivery of this Agreement and the performance of its obligations hereunder. This Agreement has been duly executed and delivered on behalf of such Party, and constitutes a legal, valid, binding obligation, enforceable against such Party in accordance with its terms.

12.1.3 All necessary consents, approvals and authorizations of all Governmental Authorities and other persons or entities required to be obtained by such Party in connection with this Agreement have been obtained.

12.1.4 The execution and delivery of this Agreement and the performance of such Party's obligations hereunder (a) do not and will not conflict with or violate any requirement of applicable Laws, regulations or orders of governmental bodies; and (b) do not and will not conflict with, or constitute a default under, any contractual obligation of such Party.

12.1.5 As of the Effective Date, there is no action or proceeding pending against such Party that questions in any material respect the validity of this Agreement or any action taken by such Party in connection with the execution of this Agreement.

12.1.6 The operation of the business of such Party and its Affiliates is being, and has been, conducted in compliance with all applicable Laws, including Compliance Laws. Neither such Party nor any of its Affiliates has received any written notice to the effect that the operation of the business of such Party or its Affiliates is not, and was not, in material compliance with any such applicable Laws, including Compliance Laws.

12.1.7 Such Party, its Affiliates and other Third Parties acting on such Party's or its Affiliates' behalf, has instituted and maintained policies and procedures designed to promote and achieve compliance with all applicable Compliance Laws. None of such Party, its Affiliates or any of their respective managing directors or employees, or, to such Party's knowledge, any of their respective Third Party representatives, partners or other Third Parties acting on such Party's or its Affiliates' behalf, has, (a) engaged in any conduct that would reasonably be expected to result in any of such Party, its Affiliates or any of their respective officers, managing directors, Third Party representatives or partners being subject to the

application of sanctions or other adverse consequences under Compliance Laws; (b) directly or indirectly, taken any action in violation of any Compliance Law; or (c) received notice of, or is otherwise aware of, any judicial or administrative proceedings involving a noncompliance with Compliance Laws.

12.1.8 None of such Party, its Affiliates or, to such Party's knowledge, its Sublicensees (in the case of RareStone) or licensees (in the case of Rhythm), or any of their respective managing directors or employees or, to such Party's knowledge, any of their respective Third Party representatives, partners or other Third Parties acting on behalf of such Party, its Affiliates or its Sublicensees (or licensees, as applicable), has, directly or indirectly, (a) taken any action in violation of Compliance Laws; (b) made, offered, authorized, facilitated, or promised any payment, contribution, gift, entertainment, bribe, rebate, kickback, financial or other advantage, or anything else of value, regardless of form or amount, to any Person in order to obtain an improper advantage, induce the recipient to violate an official or lawful duty, reward the recipient for an improper advantage already given, or for any other improper purpose, even if the payment, gift or hospitality was given to such person without an intent that it would act improperly; (c) requested, agreed to receive, or accepted a payment, gift or hospitality from a Third Party if it was known or suspected that such payment, gift or hospitality was offered with the expectation that it will obtain a business advantage for the offeror; (d) established or maintained, or is maintaining, any unlawful fund of corporate monies or properties; (e) used or is using any corporate funds for any illegal contributions, gifts, entertainment, hospitality, travel, or other unlawful expenses; (f) been or is under administrative, civil, or criminal investigation, indictment, suspension, debarment, or audit (other than a routine contract audit) by any party, in connection with alleged or possible violations of any Compliance Law; or (g) as of the date hereof received written notice from, or made a voluntary disclosure to any Governmental Authority regarding alleged or possible violations of any Compliance Law.

12.1.9 Neither such Party nor any of its Affiliates has been debarred or is subject to debarment and neither it nor any of its Affiliates will use in any capacity, in connection with the activities to be performed under this Agreement, any individual or entity that has been debarred pursuant to Section 306 of the FFDCA (or the international equivalent thereof), or who is the subject of a conviction described in such section. Each Party agrees to inform the other Party in writing immediately if it, or any individual or entity that is performing activities by or on behalf of itself hereunder, is debarred or is the subject of a conviction described in Section 306 (or the international equivalent thereof), or if any action, suit, claim, investigation or legal or administrative proceeding is pending or, to its and its Affiliates' knowledge, is threatened, relating to its, or any individual or entity that is performing activities by or on behalf of itself hereunder, debarment or conviction.

12.2 Rhythm Representations and Warranties. Rhythm hereby represents, warrants and covenants to RareStone that, as of the Effective Date:

12.2.1 Rhythm has full legal or beneficial title or ownership of, or exclusive license to the Licensed IP Rights.

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12.2.2 Rhythm has the right to grant the licenses and other rights purported to be granted herein and has not granted to any Third Party any license or other interest in the Licensed IP Rights (a) to Develop and Commercialize the Licensed Product within the RareStone Territory and the Field or (b) that would conflict with the licenses and interests granted to RareStone hereunder.

12.2.3 To Rhythm's Knowledge, there is no Third Party issued Patent that would be infringed by (a) practicing any process or method or making, using or selling any composition, which (with regard to such process, method, or composition) is claimed or disclosed in the Licensed Patents, to Commercialize the Licensed Product in the Field and in the RareStone Territory, (b) practicing any process or method or making, using or selling any composition, which (with regard to such process, method, or composition) constitutes Licensed Know-How, to Commercialize the Licensed Product in the Field and in the RareStone Territory, or (c) making, using or selling Licensed Product in the RareStone Territory.

12.2.4 To Rhythm's Knowledge, except as previously disclosed to RareStone, there is no Third Party that is infringing or misappropriating any of the Licensed IP Rights.

12.2.5 Rhythm has provided RareStone with true and correct copies (as of the Effective Date) of the Upstream Agreements in effect as of the Effective Date. Other than the Upstream Agreements, there are no agreements between Rhythm or its Affiliates and a Third Party pursuant to which Rhythm Controls any Licensed IP Rights, whether by in-license or otherwise. None of Rhythm, its Affiliates and, to Rhythm's knowledge, any Third Party, is in breach of the Upstream Agreements and none of Rhythm, its Affiliates and, to Rhythm's knowledge, any other party to the Upstream Agreements has threatened to terminate, or has otherwise alleged any material breach under, such Upstream Agreements;

12.3 Rhythm Covenant. Rhythm hereby covenants to RareStone as follows:

12.3.1 All Data provided by Rhythm hereunder shall be accurate in all material respects.

12.3.2 Subject to Section 15.5, Rhythm shall not transfer, convey or assign any of the Licensed IP Rights to any Person unless such Person agrees in writing to the applicable terms and conditions of this Agreement, and Rhythm shall use reasonable efforts to promptly notify RareStone in writing of any transfer, conveyance or assignment of any of the Licensed IP Rights.

12.3.3 Rhythm shall, and if applicable, shall cause its Affiliates to (i) comply with its obligations under the Upstream Agreements in all material respects, and not terminate the Upstream Agreements, except with RareStone's prior written approval, which shall not be unreasonably withheld; (ii) not amend or waive, or take any action or omit to take any action that would alter any of Rhythm's rights under the Upstream Agreements in any manner that would materially adversely affect, or would reasonably be expected to materially adversely

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affect, RareStone's rights under this Agreement, in each case without RareStone's prior written approval, which shall not be unreasonably withheld; and (iii) promptly notify RareStone in writing of the receipt or delivery of any notice of any default under, or termination or material amendment of, the Upstream Agreements that would materially adversely affect, or would reasonably be expected to materially adversely affect, RareStone's rights under this Agreement.

12.3.4 Rhythm shall be responsible for any payments owed to Third Parties under the Upstream Agreements existing as of the Effective Date between Rhythm and such Third Parties on account of RareStone's exploitation of Licensed Product in the Field in the Territory.

12.4 DISCLAIMER OF WARRANTIES. EXCEPT AS OTHERWISE EXPRESSLY SET FORTH IN THIS SECTION 12, NEITHER PARTY MAKES ANY REPRESENTATIONS OR WARRANTIES, EXPRESS OR IMPLIED, REGARDING THE LICENSED IP RIGHTS, LICENSED PRODUCT OR ANY OTHER MATTER, INCLUDING BUT NOT LIMITED TO ANY REPRESENTATION OR WARRANTY REGARDING MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE OR NON-INFRINGEMENT OR VALIDITY OF ANY PATENTS ISSUED OR PENDING.

13. Term and Termination.

13.1 Term. The term of this Agreement shall commence on the Effective Date and shall continue in full force and effect until the expiry of the last remaining Payment Period, unless terminated earlier pursuant to this Sections 13.2, 13.3, 13.4 or 13.5 below (such period, the "Term"). On expiration of this Agreement, the licenses granted hereunder by Rhythm to RareStone with respect to such Licensed Product and Region shall become fully paid-up, royalty fee, perpetual and irrevocable.

13.2 Termination by RareStone.

13.2.1 Prior to obtaining the MAA for the Licensed Product in the RareStone Territory, RareStone may terminate this Agreement, in its sole discretion, upon [***] prior written notice of termination to Rhythm.

13.2.2 After obtaining the MAA for the Licensed Product in the RareStone Territory, RareStone may terminate this Agreement, in its sole discretion, upon [***] prior written notice of termination to Rhythm.

13.3 Termination for Cause. Either Party may terminate this Agreement upon or after the material breach of this Agreement (including the failure to pay undisputed amounts owed) by the other Party if such Party has not cured such breach within [***] after receipt of express written notice thereof by the former Party; provided, however, if any default is not capable of being cured within such [***] period, the Parties agree on a remediation plan allowing the breaching Party to cure the breach within an additional period of [***] and the breaching Party is diligently undertaking to cure such breach in accordance with such plan, then the non-

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breaching Party shall have no right to terminate this Agreement for such breach before the end of the [***] additional cure period. If the alleged breaching Party disputes in good faith the existence or materiality of a breach specified in a notice provided by the other Party in accordance with this Section 13.3, and such alleged breaching Party provides the other Party notice of such dispute within such [***] period, then the non-breaching Party shall not have the right to terminate this Agreement under this Section 13.3 unless and until the arbitrators, in accordance with Section 15.11, have determined that the alleged breaching Party has materially breached this Agreement and that such Party fails to cure such breach within [***] following such arbitrators' decision. During the pendency of such dispute, all of the terms and conditions of this Agreement shall remain in effect and the Parties shall continue to perform all of their respective obligations hereunder.

13.4 Termination for Bankruptcy. Either Party shall have the right to terminate this Agreement upon written notice to the other Party: (a) if such other Party is declared bankrupt by a court of competent jurisdiction; (b) if a voluntary or involuntary petition in bankruptcy is filed in any court of competent jurisdiction against such other Party and such petition is not dismissed within [***] after filing; (c) if such other Party shall make or execute an assignment of substantially all of its assets for the benefit of creditors; or (d) if such other Party appoints or suffers appointment of a receiver or trustee over substantially all of its property that is not discharged within [***] after such filing.

13.5 Termination for Patent Challenge. Rhythm shall have the right to terminate this Agreement upon [***] prior written notice of termination to RareStone if RareStone, its Affiliates or its Sublicensees are parties to, or in any material respect, knowingly and willingly participate in or facilitate any action challenging the validity of the Licensed Patents ("Challenge"), unless (a) such Challenge is asserted as an affirmative defense, counterclaim, or other defensive countermeasure in respect of, a patent infringement claim brought by Rhythm against RareStone, its Affiliates or its Sublicensees (as applicable); (b) RareStone, its Affiliate or Sublicensee (as applicable) withdraws or causes to be withdrawn such Challenge within such [***] period; or (c) in the case of a Sublicensee Challenge of a Licensed Patent, RareStone terminates the sublicense, immunity or other right under the Licensed Patents granted to such Third Party within such [***] period.

14. Effect of Expiration or Termination.

14.1 Accrued Obligations. Expiration or termination of this Agreement shall not relieve the Parties of any obligation or liability accruing prior to such expiration or termination. Any termination of this Agreement shall not preclude either Party from pursuing all rights and remedies it may have under this Agreement, or at law or in equity, with respect to breach of this Agreement.

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14.2 Rights on Termination of Agreement. This Section 14.2 shall apply upon any termination (but not expiration) of this Agreement.

14.2.1 Wind-down Period. If this Agreement is terminated after the First Commercial Sale of the Licensed Product in the RareStone Territory, then RareStone, by itself or through a Sublicensee or Affiliate, shall continue to distribute the Licensed Product in the RareStone Territory during the [***] period commencing on the effective date of such termination of this Agreement in order to avoid disruption in the availability of Licensed Products to patients and to allow Rhythm to secure an alternative distributor or licensee for the Licensed Product in the RareStone Territory (the "Wind-down Period"), provided that RareStone, its Affiliates and its Sublicensees shall cease such activities, or any portion thereof, in the RareStone Territory, upon [***] written notice by Rhythm requesting that such activities, or any portion thereof, be ceased. Promptly after such [***] period, RareStone shall sell to Rhythm, and Rhythm shall purchase, any quantities of Licensed Product in good condition, with a sufficient remaining shelf life (no less than [***]) at the transfer price paid by RareStone for such Licensed Product. Notwithstanding any other provision of this Agreement, during the Wind-down Period, RareStone's, its Sublicensees' and its and their respective Affiliates' rights with respect to the Licensed Product (including the Licensed Marks) in the RareStone Territory shall be non-exclusive and, without limiting the foregoing, Rhythm shall have the right to engage one or more other distributor(s) and/or licensee(s) of the Licensed Product in all or part of the RareStone Territory. Any Licensed Product sold or disposed by RareStone, its Affiliates and Sublicensees in the RareStone Territory during the Wind-down Period shall be subject to applicable payment obligations under Section 7 above.

14.2.2 Assignment of Regulatory Filings and Registrations. RareStone shall assign (or cause to be assigned) to Rhythm or its designee (or to the extent not so assignable, RareStone shall take all reasonable actions requested by Rhythm to make available to Rhythm or its designee the benefits of) all Regulatory Filings and Registrations for the Licensed Product in the RareStone Territory, including any such Regulatory Filings or Registrations made or owned by its Affiliates and/or Sublicensees, and all domain names owned by RareStone for the Licensed Product. In each case, unless otherwise required by any applicable Law or regulation or requested by Rhythm, the foregoing assignment (or availability) shall be made within [***] after the effective date of any termination of this Agreement.

14.2.3 Data and RareStone Product Know-How. At Rhythm's request, RareStone shall provide to Rhythm a copy of all Data and RareStone Product Know-How (including without limitation a copy of RareStone's list of customer hospitals), to the extent not previously provided to Rhythm and permitted to be provided by the applicable Laws and regulations relating to the protection of personal information, and, subject to the terms of this Section 14.2.3, Rhythm shall have the right to use all Data and RareStone Product Know-How following termination of this Agreement solely within the Field and solely to Commercialize the Licensed Product anywhere in the world. RareStone shall have the right to redact all confidential information and data from such Data and RareStone Product Know-How to the extent such information or data relates to any other products or services or RareStone's confidential actual or planned business or operations.

[***] Certain information in this document has been excluded pursuant to Regulation S-K, Item (601)(b)(10). Such excluded information is both (i) not material and (ii) the type that the Registrant treats as private or confidential.

14.2.4 Assignment of Contract Manufacturers Agreements. At Rhythm's request, RareStone shall use Commercially Reasonable Efforts to assign (or cause to be assigned) to Rhythm or its designee all agreements entered into between RareStone and CMOs for the Manufacture and supply of Licensed Product in the RareStone Territory, with the same financial conditions, in order to ensure continuity of supply. In each case, unless otherwise requested by Rhythm, the foregoing assignments shall be made within [***] after the effective date of any termination of this Agreement.

14.2.5 Transition. RareStone shall reasonably cooperate with Rhythm, and/or its designee to transition the development, sale and ongoing marketing, promotion and Commercialization of the Licensed Product in the RareStone Territory during the Wind-down Period. RareStone shall, upon written request from Rhythm, notify its customers of such transition and shall reasonably assist such customers in ordering Licensed Product from Rhythm or its designee. Without limiting the foregoing, RareStone shall use reasonable efforts to conduct in an expeditious manner any activities to be conducted under this Section 14.2.

14.2.6 Licenses. Effective as of the date of the Wind-down Period and subject to the terms of this Section 14.2.6, RareStone hereby grants to Rhythm an exclusive, fully paid-up, royalty-free, worldwide, transferable, perpetual and irrevocable license, with the right to grant sublicenses, under any intellectual property rights owned or Controlled by RareStone that are necessary to make, use, sell, offer for sale, or import the Licensed Products within the RareStone Territory as they exist at the time of such termination of this Agreement.

14.2.7 Return of Materials. Within [***] after the end of the Wind-down Period, upon request by Rhythm, RareStone shall either return to Rhythm or destroy all tangible items comprising, bearing or containing the Licensed Marks, any trade names or trademarks owned by Rhythm, Licensed Product samples, literature, sales and promotional aids ("Product Materials"), that are in RareStone's possession. Effective upon the end of the Wind-down Period, RareStone shall cease to use all trademarks and trade names of Rhythm (including the Licensed Marks) in the RareStone Territory, and all rights granted to RareStone hereunder with respect to the Licensed Product in the RareStone Territory shall terminate. Upon the effective date of the termination of this Agreement for any reason, upon the written request of a Party, the non-requesting Party shall either, at the requesting Party's election: (a) promptly destroy all copies of such Confidential Information in the possession or control of the non-requesting Party and confirm such destruction in writing to the requesting Party; or (b) promptly deliver to the requesting Party, [***], all copies of such Confidential Information in the possession or control of the non-requesting Party. Notwithstanding the foregoing, the non-requesting Party shall be permitted to retain such Confidential Information (i) to the extent reasonably necessary for purposes of performing any continuing obligations or exercising any ongoing rights hereunder and, in any event, a single copy of such Confidential Information for archival purposes and (ii) any computer records or files containing such Confidential Information that have been created solely by such non-requesting Party's automatic archiving and back-up procedures, to the extent created and retained in a manner consistent with such non-requesting Party's standard archiving and back-up procedures, but not for any other uses or purposes. All Confidential

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Information shall continue to be subject to the terms of this Agreement for the period set forth in Section 9.1.

14.2.8 Sublicenses. Upon any termination of this Agreement, Rhythm shall be entitled, in its sole discretion, to grant a direct license to any Sublicensee of RareStone hereunder having the same scope as such sublicense and on terms and conditions no less favorable to such Sublicensee than the terms and conditions of this Agreement, provided that such Sublicensee is not in default of any applicable obligations under this Agreement and agrees in writing to be bound by the terms and conditions of such direct license.

14.2.9 No Renewal, Extension or Waiver. Acceptance of any order from, or sale or license of, any Licensed Product to RareStone after the notice or effective date of expiration or termination of this Agreement in its entirety shall not be construed as a renewal or extension hereof, or as a waiver of expiration or termination of this Agreement in its entirety.

14.2.10 Costs and Expenses. [***] Any out-of-pocket costs and expenses incurred by a Party but to be borne by the other Party pursuant to this Section 14.2.10 shall be reimbursed within [***] after the Party responsible for such costs and expenses receives an invoice from the other Party therefor (which invoice shall be accompanied by documentation supporting the calculation of amounts to be so reimbursed).

14.3 Survival. Upon termination or expiration of this Agreement, all rights and obligations of the Parties under this Agreement shall be terminated except those described in the following Sections: 8, 9, 10.1, 12.4, 14.1, 14.2, this 14.3 and 15. In addition, upon expiration of the Term (but not termination), the licenses granted to RareStone hereunder will survive and will automatically become non-exclusive, perpetual, irrevocable, fully paid-up, non-assessable and non-royalty bearing.

15. Miscellaneous.

15.1 RareStone Obligations. Notwithstanding anything herein to the contrary, RareStone may fulfill its obligations hereunder by or through its Affiliates, its Sublicensees, or any of its or their respective (sub)contractors.

15.2 Public Announcements. Neither Party shall make any public announcements concerning matters concerning this Agreement or the negotiation thereof without the prior written consent of the other party unless such disclosure is required by law, in which case the announcing party shall provide the other party with reasonable notice of such disclosure.

15.3 Insurance.

15.3.1 Each Party shall secure and maintain in effect, during the Term of this Agreement and for a period of [***] thereafter, comprehensive general liability insurance (including product liability insurance), underwritten by a reputable insurance carrier, in a form and having liability limits standard and customary for entities in the pharmaceutical industry

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based on such Party's activities and location and indemnification obligations under this Agreement.

15.3.2 Each Party shall furnish to the other Party, on request, certificates of insurance setting forth the amount of liability insurance and shall provide the other Party at least [***] written notice prior to any termination or material reduction to the level of coverage, unless a replacement insurance policy that complies with this Section 15.3 is in place before such termination or material reduction.

15.4 Force Majeure. If the performance of any part of this Agreement by either Party is prevented, restricted, interfered with or delayed by reason of any cause beyond the reasonable control of such Party, regardless of whether such cause is foreseeable as of the Effective Date or thereafter (including, fire, flood, earthquake, tsunami, embargo, power shortage or failure, acts of war, insurrection, riot, terrorism, strike, lockout or other labor disturbance, acts of God, epidemic, pandemic (including COVID-19) or any acts, omissions or delays in acting of the other Party), the Party so affected shall, upon giving written notice to the other Party within [***] of the occurrence of such cause, be excused from such performance to the extent of such prevention, restriction, interference or delay; provided that the affected Party shall use its commercially reasonable efforts to avoid or remove such causes of non-performance and shall continue performance with the utmost dispatch whenever such causes are removed.

15.5 Assignment. Neither Party shall assign its rights or obligations under this Agreement without the prior written consent of the other Party; provided, however, that a Party may, without such consent, assign this Agreement and its rights and obligations hereunder (a) to any Affiliate, or (b) in connection with the transfer or sale of all or substantially all of its business to which this Agreement relates, or in the event of its merger, consolidation, change in control or similar transaction. Notwithstanding the foregoing, in the event of any assignment of this Agreement by a Party, intellectual property rights owned or controlled by the other party to such transaction shall not be included in the technology licensed or assigned by such Party hereunder so long as such intellectual property rights are not practiced by the affected Party in the course of performing its obligations under this Agreement. Any permitted assignee shall assume all obligations of its assignor under this Agreement. Any purported assignment in violation of this Section 15.5 shall be void.

15.6 Severability. If any term or other provision of this Agreement is held to be invalid, illegal or incapable of being enforced in accordance with the terms hereunder, all other conditions and provisions of this Agreement will nevertheless remain in full force and effect so long as the economic or legal substance of the transaction contemplated by this Agreement is not affected in any manner materially adverse to either Party. Upon any such determination, the Parties shall negotiate in good faith to modify this Agreement so as to effect their original intent as contemplated by this Agreement to the greatest extent possible.

15.7 Relationship of the Parties. For all purposes of this Agreement, Rhythm and RareStone shall be deemed to be independent entities and anything in this Agreement to the contrary notwithstanding, nothing herein shall be deemed to constitute Rhythm and RareStone as

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partners, joint ventures, co-owners, an association or any entity separate and apart from each Party itself, nor shall this Agreement constitute any Party hereto an employee or agent, legal or otherwise, of the other Party for any purposes whatsoever. Neither Party is authorized to make any statements nor representations on behalf of the other Party or in any way obligate the other Party, except as expressly authorized in writing by the other Party.

15.8 Interpretation. The headings set forth at the beginning of the various Sections of this Agreement are for reference and convenience and shall not affect the meanings of the provisions of this Agreement. Whenever the context may require, any pronoun shall include the corresponding masculine, feminine and neuter forms. The words "include" and "contain" (and their variant forms) shall be deemed to be followed by the phrase "without limitation." The word "will" shall be construed to have the same meaning and effect as the word "shall." "Dollar" or "$" as used in this Agreement means the lawful currency of the United States. Any reference to any laws, codes or regulations herein shall be construed as referring to such laws as from time to time enacted, repealed or amended. The words "herein," "hereof" and "hereunder," and words of similar import, shall be construed to refer to this Agreement in its entirety and not to any particular provision hereof. Any reference herein to any Person shall be construed to include the Person's permitted successors and assigns. Each accounting term used herein that is not specifically defined herein shall have the meaning given to it under generally accepted cost accounting principles, but only to the extent consistent with its usage and the other definitions in this Agreement.

15.9 Governing Law. This Agreement shall be governed by and construed in accordance with the laws of the State of New York, without regard to the conflicts of law principles thereof.

15.10 Dispute Resolution. The Parties recognize that disputes may from time to time arise relating to or in connection with this Agreement, including the Parties' rights and obligations hereunder. The Parties agree that, except as otherwise provided in Section 6.1.5, if a dispute arises out of or relating to this Agreement, including without limitation, any alleged breach of this Agreement or any issue relating to the interpretation or application of this Agreement, and the Parties are unable to resolve such dispute within [***] after such dispute is first identified by either Party in writing to the other, the Parties shall refer such dispute to the Senior Executives for attempted resolution by good faith negotiations within [***] after such notice is received. If the dispute is not resolved within such [***], the dispute shall be finally resolved by arbitration in accordance with Section 15.11, and thereafter neither Party shall have any further obligation under this Section 15.10. Any disputes concerning the propriety of the commencement of arbitration shall be finally settled by the arbitral tribunal. Notwithstanding the foregoing, and without waiting for the expiration of any such [***], each Party shall have the right to apply to any court of competent jurisdiction for appropriate interim or provisional relief, as necessary to protect the rights or property of such Party.

15.11 Arbitration. If the Parties are unable to resolve any disputes arising under or in connection with this Agreement as described above in Section 15.10, then, all such disputes shall be submitted to and finally settled by the International Court of Arbitration of the

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International Chamber of Commerce in accordance with the current Rules of Arbitration of the International Chamber of Commerce as then in effect by one or more arbitrators appointed in accordance with said Rules. The seat, or legal place, of arbitration shall be New York City, New York, USA. The language to be used in the arbitral proceedings will be English. The arbitration award shall be final and binding on the Parties, and the Parties undertake to carry out any award without delay. Judgment upon the award rendered by such arbitrator(s) may be entered by any court or forum having jurisdiction. The content of all arbitration proceedings and any rulings or awards of the arbitrator(s) under this Section 15.11 shall be deemed Confidential Information of both Parties; provided that in addition to disclosures permitted by Section 9.3, disclosure shall be authorized (i) to the extent required to protect or pursue a legal right, or enforce or challenge an award in bona fide legal proceedings before a state court or other judicial authority, (ii) where needed for the preparation or presentation of a claim or defense in the arbitration, or (iii) by order of the arbitral tribunal upon application of a Party. Notwithstanding the Parties' agreement to arbitrate, unless the Parties agree in writing in any particular case, claims and disputes between the Parties relating to or arising out of, or for which resolution depends in whole or in part on a determination of the interpretation, scope, validity, enforceability or infringement of any Patents shall not be subject to arbitration under this Agreement, and the Parties may pursue whatever rights and remedies may be available to them under law or equity, including litigation in a court of competent jurisdiction, with respect to such claims and disputes.

15.12 Entire Agreement; Amendment. This Agreement, together with the Exhibit(s) hereto, the Trademark License, the Clinical Supply Agreement, the Commercial Supply Agreement, the Quality Agreement and the Pharmacovigilance & Safety Agreement, and each additional document, instrument or other agreement to be executed and delivered pursuant hereto, constitute all of the agreements of the Parties with respect to, and supersede all prior agreements and understandings relating to the subject matter of, this Agreement or the transactions contemplated by this Agreement. This Agreement may not be modified or amended except by a written instrument specifically referring to this Agreement signed by the Parties hereto.

15.13 Waiver. No waiver by one Party of the other Party's obligations, or of any breach or default hereunder by any other Party, shall be valid or effective, unless such waiver is set forth in writing and is signed by the Party giving such waiver; and no delay in enforcing a Party's rights under this agreement or such waiver shall be deemed a waiver of any subsequent breach or default of the same or similar nature or any other breach or default by such other Party.

15.14 Notices. Any consent, notice or report required or permitted to be given or made under this Agreement by a Party to the other Party shall be in writing, in the English language, shall expressly reference the section(s) of this Agreement to which they pertain, and shall be delivered to the other Party, effective on receipt at the appropriate address set forth below or to such other addresses as may be designated in writing by the Parties from time to time during the term of this Agreement:

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If to Rhythm: Rhythm Pharmaceuticals Inc.
222 Berkeley Street, 12th Floor
Boston, MA, USA, 02116
Attention: Chief Executive Officer

If to RareStone: RareStone Inc.
1 Main Street, 13th Floor
Cambridge, MA 02142
Attention: [***]
Email: [***]

With a copy to:

Cooley LLP
500 Boylston Street
14th Floor
Boston, MA 02116
Attention: [***]
Email: [***]

15.15 Counterparts. This Agreement may be executed in separate counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

[SIGNATURE PAGE FOLLOWS.]

IN WITNESS WHEREOF, each Party has caused a duly authorized representative to execute and deliver this Exclusive License Agreement as of the Effective Date.

Rhythm Pharmaceuticals Inc.

By: _____
Name: _____
Title: _____

RareStone Group Ltd.

By: _____
Name: _____
Title: _____

[Signature Page to Exclusive License Agreement]

EXHIBIT A
LICENSED MARKS

- [***]

EXHIBIT B
LICENSED PATENTS

[***]

EXHIBIT C
SETMELANOTIDE

[***]

EXHIBIT D
CLINICAL DEVELOPMENT PLAN

[***]

[***]

[***]

[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]

[***]

[***]	[***]
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[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]

EXHIBIT E
COMMERCIALIZATION PLAN

[***]

EXHIBIT F
EQUITY AGREEMENT

[***]

EXHIBIT G
PRESS RELEASE

Rhythm Pharmaceuticals and RareStone Ltd. Announce Exclusive Licensing Agreement for the Development and Commercialization of IMCIVREE (setmelanotide) in China

-- RareStone to seek marketing authorization for IMCIVREE to treat obesity due to biallelic POMC, PCSK1 and LEPR deficiencies and Bardet-Biedl and Alström syndromes in mainland China, Hong Kong and Macau –
-- Rhythm to receive $12 million upfront in cash and equity, up to $63.5 million in future milestone payments and sales royalties --

BOSTON, December 6, 2021 -- Rhythm Pharmaceuticals, Inc. (Nasdaq: RYTM), a biopharmaceutical company aimed at developing and commercializing therapies for the treatment of rare genetic diseases of obesity, and RareStone LTD, formerly Citrine Medicine, a China-based rare disease company, today announced an exclusive licensing agreement for the development and commercialization of IMCIVREE® (setmelanotide) in China, including mainland China, Hong Kong and Macau. This licensing agreement marks the first expansion of Rhythm's pipeline into Asia and is designed to accelerate patient access to IMCIVREE where there remains significant unmet need to address the severe, early-onset obesity and hyperphagia that characterize both acquired and genetic diseases of the melanocortin-4 receptor (MC4R) pathway.

According to the terms of the agreement, RareStone will seek local approvals to commercialize IMCIVREE for the treatment of obesity and hyperphagia due to biallelic proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency, as well as Bardet-Biedl and Alström syndromes. Additionally, RareStone will fund efforts to identify and enroll patients from China in Rhythm's global EMANATE trial, a Phase 3, randomized, double-blind, placebo-controlled trial to evaluate setmelanotide in five independent sub-studies in patients with obesity due to a heterozygous variant of POMC/PCSK1 or LEPR; certain variants of the SRC1 gene, certain variants of the SH2B1 gene, or PCSK1 N221D deletions within the MC4R pathway.

"RareStone, a company committed to treating rare diseases, is well-positioned to leverage its network of hospitals and key opinion leaders, deep regulatory experience and community-building infrastructure to advance IMCIVREE through clinical development and regulatory approvals in China," said David Meeker, M.D., Chair, Chief Executive Officer and President of Rhythm. "We are thrilled to enter into this agreement, which substantially accelerates our ability to address the needs of patients living in China and potentially make IMCIVREE available to many more patients with rare genetic diseases of obesity."

RareStone was founded in 2019 with funding from leading health care investors, including Eight Roads, F-Prime Capital, Vivo Capital, Quan Capital, 3H Health Investment and WU Capital. The Shanghai-based company is focused on building an ecosystem to support patients and families living with rare diseases in Greater China and has dedicated itself to improving the lives of patients with rare and intractable diseases by making diagnosis and essential treatments available and accessible to those who need them.

“There is a significant need in China for a therapeutic option to treat patients with early-onset, severe obesity and hyperphagia caused by variants in genes of the MC4R pathway,” said Shawn Xiang, Ph.D., CEO of RareStone. “Rhythm’s precision medicine, IMCIVREE (setmelanotide), approved by FDA and authorized by the European Commission and Great Britain’s Medicines & Healthcare Products Regulatory Agency, has transformed the treatment paradigm for rare genetic diseases of obesity. We are eager to deliver the proven clinical benefit of IMCIVREE to patients in China and plan to pursue local approvals rapidly in five initial indications, while supporting Rhythm’s ongoing clinical development efforts more broadly.”

According to the terms of the licensing agreement, RareStone will make an upfront payment to Rhythm of $7 million and issue $5 million in equity to Rhythm. Rhythm will be eligible to receive development and commercialization milestones of up to $63.5 million, as well as tiered royalty payments on annual net sales of IMCIVREE.

About Rhythm Pharmaceuticals

Rhythm is a commercial-stage biopharmaceutical company committed to transforming the treatment paradigm for people living with rare genetic diseases of obesity. Rhythm’s precision medicine, IMCIVREE (setmelanotide), was approved in November 2020 by the U.S. Food and Drug Administration (FDA) 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 and in July and September 2021, respectively, by the European Commission (EC) and Great Britain’s Medicines & Healthcare Products Regulatory Agency (MHRA) for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. IMCIVREE is the first-ever FDA-approved and EC- and MHRA-authorized therapy for patients with these rare genetic diseases of obesity. The Company submitted a supplemental New Drug Application (sNDA) to the FDA, which was accepted for filing in November 2021 and assigned a Prescription Drug User Fee Act (PDUFA) goal date of March 16, 2022. Rhythm also submitted a Type II variation application to the European Medicines Agency in October 2021 seeking regulatory approval and authorization for setmelanotide to treat obesity and control of hunger in adult and pediatric patients 6 years of age and older with BBS or Alström syndrome in both the United States and European Union. Additionally, Rhythm, along with its partners, is advancing a broad clinical development program for setmelanotide in other rare genetic diseases of obesity and is leveraging the Rhythm Engine, the largest known obesity DNA database -- now with approximately 45,000 sequencing samples -- to improve the understanding, diagnosis and care of people living with severe obesity due to certain genetic deficiencies. Rhythm’s headquarters is in Boston, MA.

About RareStone LTD.
RareStone, formerly Citrine Medicine, is dedicated to improving the lives of patients with rare and intractable diseases by making diagnosis and essential treatments available and accessible to those who need them in Greater China. Our mission is to build the first rare disease ecosystem in China, and in doing so, enable people with rare diseases to live more normal lives. In addition to developing and marketing rare disease drugs, RareStone aims to establish a patient-centric platform which educates people on rare diseases, trains doctors on diagnosis and treatment, and helps doctors develop a full disease management protocol. RareStone's lead product candidate, Wakix® (pitolisant), is an investigational oral drug in development for the treatment of narcolepsy and obstructive sleep apnea in China. RareStone also recently announced two strategic partnerships that will gives the company exclusive Greater China rights to develop, register, and commercialize Alkindi® for pediatric congenital adrenal hyperplasia (CAH) patients and Efmody® for adolescent and adult CAH and adrenal insufficiency patients. RareStone is headquartered in Shanghai, China and has other offices in Beijing, China and Cambridge, Mass. For more information, visit www.rarestonegroup.com

IMCIVREE® (setmelanotide) Indication
In the United States, IMCIVREE is indicated for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency confirmed by an FDA-approved genetic test demonstrating variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS).

In the EU and Great Britain, IMCIVREE is indicated for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. IMCIVREE should be prescribed and supervised by a physician with expertise in obesity with underlying genetic etiology.

Limitations of Use
IMCIVREE is not indicated for the treatment of patients with the following conditions as IMCIVREE would not be expected to be effective:

- Obesity due to suspected POMC, PCSK1, or LEPR deficiency with *POMC*, *PCSK1*, or *LEPR* variants classified as benign or likely benign;
- Other types of obesity not related to POMC, PCSK1 or LEPR deficiency, including obesity associated with other genetic syndromes and general (polygenic) obesity.

Important Safety Information

WARNINGS AND PRECAUTIONS

Disturbance in Sexual Arousal: Sexual adverse reactions may occur in patients treated with IMCIVREE. Spontaneous penile erections in males and sexual adverse

reactions in females occurred in clinical studies with IMCIVREE. Instruct patients who have an erection lasting longer than 4 hours to seek emergency medical attention.

Depression and Suicidal Ideation: Some drugs that target the central nervous system, such as IMCIVREE, may cause depression or suicidal ideation. Monitor patients for new onset or worsening of depression. Consider discontinuing IMCIVREE if patients experience suicidal thoughts or behaviors.

Skin Pigmentation and Darkening of Pre-Existing Nevi: IMCIVREE may cause generalized increased skin pigmentation and darkening of pre-existing nevi due to its pharmacologic effect. This effect is reversible upon discontinuation of the drug. Perform a full body skin examination prior to initiation and periodically during treatment with IMCIVREE to monitor pre-existing and new skin pigmentary lesions**.**

Risk of Serious Adverse Reactions Due to Benzyl Alcohol Preservative in Neonates and Low Birth Weight Infants: IMCIVREE is not approved for use in neonates or infants.

ADVERSE REACTIONS

- The most common adverse reactions (incidence ≥23%) were injection site reactions, skin hyperpigmentation, nausea, headache, diarrhea, abdominal pain, back pain, fatigue, vomiting, depression, upper respiratory tract infection, and spontaneous penile erection.

USE IN SPECIFIC POPULATIONS

Discontinue IMCIVREE when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus.

Treatment with IMCIVREE is not recommended for use while breastfeeding.

To report SUSPECTED ADVERSE REACTIONS, contact Rhythm Pharmaceuticals at +1 (833) 789-6337 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See U.S. Full Prescribing Information, EU SmPC and MHRA SmPC for IMCIVREE.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this press release that do not relate to matters of historical fact should be considered forward-looking statements, including without limitation statements regarding activities in connection with the exclusive licensing agreement with RareStone and potential payments thereunder, the potential, safety, efficacy, and regulatory and clinical progress of setmelanotide, including the anticipated timing for initiation of clinical trials and

release of clinical trial data and our expectations surrounding potential regulatory submissions, approvals and timing thereof, and our business strategy and plans, including regarding commercialization of setmelanotide. Statements using word such as "expect", "anticipate", "believe", "may", "will" and similar terms are also forward-looking statements. Such statements are subject to numerous risks and uncertainties, including, but not limited to our ability to enroll patients in clinical trials, the design and outcome of clinical trials, the impact of competition, the ability to achieve or obtain necessary regulatory approvals, risks associated with data analysis and reporting, our liquidity and expenses, the impact of the COVID-19 pandemic on our business and operations, including our preclinical studies, clinical trials and commercialization prospects, and general economic conditions, and the other important factors discussed under the caption "Risk Factors" in our Quarterly Report on Form 10-Q for the quarter ended September 30, 2021 and our other filings with the Securities and Exchange Commission. Except as required by law, we undertake no obligations to make any revisions to the forward-looking statements contained in this release or to update them to reflect events or circumstances occurring after the date of this release, whether as a result of new information, future developments or otherwise.

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CONSULTING AGREEMENT

This Consulting Agreement (this "Agreement") is entered effective as of this 11th day of September, 2021 (the "Effective Date") between Rhythm Pharmaceuticals, Inc., a Delaware corporation located at 222 Berkeley Street, Suite 1200, Boston, MA 02116 (the "Company"), and Murray Stewart, D.M., F.R.C.P. (the "Consultant"), residing or having a principal place of business at _____ (each, a "Party" and collectively, the "Parties").

RECITALS

WHEREAS, the Consultant and the Company are party to an offer letter dated as of Setptember 14, 2018 (the "Offer Letter");

WHEREAS, the Consultant terminated employment as the Company's Chief Medical Officer as of September 10, 2021 (the "Separation Date") without Good Reason (as defined in the Offer Letter), it being understood and agreed by the Parties that the Consultant will not be entitled to the severance payments and benefits set forth in the Offer Letter; and

WHEREAS, the Company, on behalf of itself and its subsidiaries and successors, whether now existing or hereafter acquired or established (severally and collectively, the "Company") desires to obtain the services of the Consultant, and the Consultant is willing to render services upon the terms and conditions set forth below.

NOW, THEREFORE, in consideration of the mutual promises contained herein, the Company and the Consultant hereby agree as follows:

ARTICLE 1. ENGAGEMENT AND SCOPE OF WORK

1.1. Engagement. Subject to the following terms and conditions, the Company hereby retains the Consultant to perform such consulting and advisory services related to the Consultant's area of work experience and expertise as the Company may from time to time reasonably request (the "Services") and the Consultant accepts such engagement. All Services to be performed by the Consultant for the Company shall be under the general supervision of the Company. The Services may be sought by the Company over the telephone, in writing or by email, or in person at the Company or at the Consultant's offices or laboratory or in other locations as mutually agreed upon.

1.2. Commitment. The Consultant agrees to be available to render the Services from time to time as requested by the Company at such times and locations as may be mutually agreed by the Parties. The Consultant shall devote at least twelve (12) hours per week to the performance of the Services. The Consultant shall devote reasonable commercial efforts to the performance of the Services, and shall perform them in accordance with all applicable laws and regulations, and consistent with current industry standards relative to such Services.

1.3. Nature of Relationship. The Parties acknowledge and agree that, subject to Section 4.1 and the other remaining provisions of this Agreement, the Consultant is entering into a non-exclusive consulting relationship with the Company.

ARTICLE 2. COMPENSATION

2.1. Consulting Fees. For all Services provided under this Agreement, the Company will pay the Consultant a monthly fee of $12,000 per month, prorated for any partial month of service and payable monthly in arrears. The Consultant acknowledges and confirms that the Consultant has been selected to serve as a Consultant because of expertise in the relevant subject matter. Nothing in this Agreement is intended to be, or construed as, a reward for past or incentive for future decisions regarding prescribing, purchasing, using, recommending preferential formulary status, or dispensing any Company product. The Parties represent and warrant that the compensation described in this Section 2 was determined by the Parties through good faith and arms-length bargaining, constitutes fair market value for the Services, and has not been determined in a manner that takes into account the volume or value of any business between the Parties or as an inducement to generate business for Company. The Parties further acknowledge and agree that the Consultant shall continue to make all treatment and prescribing decisions (including prescribing products) solely in accordance with independent medical and clinical judgment, and that such decisions shall not be affected by this Agreement, the payments made hereunder or the relationship created hereby.

2.2. Expenses. Travel and related expenses incurred by the Consultant in connection with the performance of Services under this Agreement will be reimbursed at actual cost by the Company. No reimbursement will be made for any expenses incurred by the Consultant during the performance of Services under this Agreement unless such expenses are approved in advance by the Company. All approvals by the Company must be given or confirmed in writing; expense approvals can be requested from the Chief Executive Officer or any Vice President of the Company.

2.3. Equity Awards. Schedule A to this Agreement sets forth each option to purchase shares of the Company's common stock (each, an "Option") and restricted stock unit award of the Company held by the Consultant (each, an "RSU Award" and together with the Options, the "Equity Awards"), in each case, as of the Separation Date. There shall be no break in service as a result of the occurrence of the Separation Date and the Consultant's commencement of Services under this Agreement for purposes of the Equity Awards. However, notwithstanding anything to the contrary in the agreements evidencing the Equity Awards, and subject to Section 7.1 below, Consultant acknowledges and agrees that (i) as of the Separation Date, each Equity Award was vested as to the number of shares shown under the heading "Vested Shares" set forth on Exhibit A ("Vested Shares"); (ii) each RSU Award shall remain eligible to vest during the Consulting Period with respect to the number of shares shown under the heading "Shares Eligible to Vest" set forth on Exhibit A ("Shares Eligible to Vest") in accordance with its original vesting schedule and subject to the Consultant's continued Services under this Agreement through the applicable vesting date(s); (iii) the portion of each Equity Award that covers neither Vested Shares nor Shares Eligible to Vest was forfeited and terminated for no consideration as of the Separation Date; and (iv) the portion of each Option covering Vested Shares will remain outstanding and exercisable until the earlier of (A) the final expiration date of the Option set forth in the documents governing the Option and (B) the expiration of three months following the termination of the Services (provided that the Option will remain subject to earlier termination in connection with a corporate transaction or event in accordance with the documents governing the Option).

2.4. 2021 Bonus. The Company shall pay to the Consultant an amount in cash equal to the annual bonus the Consultant would have earned for 2021 had the Consultant remained employed by the Company, as determined by the Company's board of directors in its discretion based on actual performance achieved, multiplied by a fraction (a) the numerator of which is (i) nine (9) plus (ii) the product of thirty percent (30%) and the number of months the Consultant provides the Services hereunder during the fourth quarter of 2021, and (b) the denominator of which is twelve (12). Such amount shall be paid to the Consultant, less applicable withholdings, when 2021 bonuses are paid in the ordinary course to actively employed senior executives of the Company, but in no event later than March 15, 2022.

2.5. Other. Any other future compensation, including equity awards or fees, shall be determined in the discretion of the Company and/or the Board.

ARTICLE 3. THIRD PARTY RESTRICTIONS AND POLICIES

3.1. Absence of Restrictions. The Consultant represents and warrants that the Consultant is presently under no contractual or other restrictions or obligations which are inconsistent with the Consultant's execution of this Agreement or the performance of the Services hereunder, and during the term of this Agreement, the Consultant agrees not to enter into any agreement, either written or oral, that conflicts with the obligations under this Agreement. The Consultant represents and warrants that the performance of all the terms of this Agreement does not and will not breach any agreement or obligation to keep in confidence proprietary information acquired by the Consultant from any third party in confidence or in trust. The Consultant agrees not to divulge to the Company any trade secrets, know-how, confidential information, or other proprietary intellectual property, including any such items that the Consultant may have acquired from or developed for any third party, in violation of any agreement between the Consultant and such third party.

ARTICLE 4. DISCLOSURES, NON-COMPETITION, AND NON-SOLICITATION

4.1. Disclosures. The Consultant agrees to fully disclose his/her relationship with Company contemplated in this Agreement, consistent with requirements of any healthcare institution, medical committee, or other medical or scientific organization with which the Consultant is affiliated. If the Consultant is or becomes a member of a committee of a third party that is responsible for setting formularies or developing clinical practice guidelines affiliated with any healthcare institute, medical committee, or other scientific organization (collectively, "Committee"), The Consultant agrees to comply with all disclosure obligations to such Committee and shall disclose to said Committee the existence and nature of the Consultant's relationship with Company without breaching any obligations of confidentiality to Company as provided under the Agreement. Upon disclosure, the Consultant shall follow the procedures set forth by the Committee of which the Consultant is a member (e.g., recusing oneself from decisions relating to the product for which the Consultant has provided services to Company). The Consultant represents and warrants that the Consultant has fully complied with any obligations of its current place of employment or applicable institutional affiliations to disclose and obtain prior written approval of the Consultant's acting as a consultant for Company and of the duties required of the Consultant under this Agreement.

4.2. Non-Competition. The Consultant understands the confidential nature of the information and materials that the Consultant will acquire or develop in performing Services under this Agreement. The Consultant acknowledges that if such information or materials were revealed to competitors of the Company, then such disclosure could cause damage to the Company. Therefore, the Consultant acknowledges and agrees that, for the duration of the term of this Agreement, the Consultant shall not engage in any activity that would constitute a conflict of interest with the Company, and shall not assist any other person or entity that competes or intends to compete with the Company and any other specific programs agreed to in writing by the Parties. The Consultant agrees to notify Company in writing prior to performing any services for or on behalf of a drug compendia organization which relates to a Company product. The Company reserves the right to terminate services in the event that the Company determines, in its sole discretion, that such compendia-related activities pose a potential conflict of interest with the Consultant's Services for Company. The Consultant agrees that, until the later of the termination of this Agreement or the first anniversary of the Separation Date, the Consultant will not, directly or indirectly, as an officer, director, manager, employee, consultant, advisor, owner, partner, member, stockholder, or in any other capacity, (a) compete with the business or planned business of the Company or any of its subsidiaries or controlled affiliates, or (b) take any steps or actions to facilitate or prepare for competition with the business or planned business of the Company or any of its subsidiaries or controlled affiliates, nor will the Consultant assist another person to take any action that the Consultant would be prohibited from taking under this Section 4.2. The obligations not to compete that the Consultant has undertaken under this Section 4.2 shall apply in all countries of the world. For purposes of this Section 4.2, the Consultant will not be deemed or treated as being in competition with the business or planned business of the Company or any of its subsidiaries or controlled affiliates or as being in violation of the covenant set forth in the clause (b) above in this Section 4.2 merely by virtue of the Consultant's ownership of any equity interest in any business or person that is in competition with, or is planning to be in competition with, the business or planned business of the Company or any of its subsidiaries or controlled affiliates, if my ownership of any such equity interest represents five percent (5%) or less the total equity interests in such business or person. The Consultant hereby acknowledges and agrees that the foregoing restrictions contained in this Section 4.2 are reasonable, proper and necessitated by the legitimate business interests of the Company and will not prevent the Consultant from earning a living or pursuing the Consultant's career. In the event that a court finds this Section 4.2, or any of its restrictions, to be unenforceable or invalid, the Consultant and the Company agree that (i) this Section 4.2 will be automatically modified to provide the Company with the maximum protection of its business interests allowed by law and (ii) the Consultant shall be bound, and such court shall enforce, this Section 4.2 as so modified. The parties agree that for the purposes of this Agreement, "business" shall mean development of MC4R agonists for the treatment of human disease. The Consultant has seven business days following the Consultant's execution of this Agreement to revoke this Agreement by delivering written notice to the General Counsel of the Company.

4.3. Non-Solicitation. The Consultant further acknowledges and agrees that, for the duration of the term of this Agreement and for one (1) year thereafter, the Consultant shall not directly or indirectly (a) solicit, hire or engage, or attempt to solicit, hire or engage, any individual as an employee, consultant, advisor, officer, manager, managing partner, director or in any other similar capacity if such individual shall have been an employee of the Company or any of its subsidiaries or controlled affiliates at any time during the one (1) year period prior to the

Separation Date; (b) solicit, induce or attempt to induce any customer, vendor, contractor, consultant or advisor of the Company or any of its subsidiaries or controlled affiliates to terminate, diminish, or materially alter his, her or its relationship with the Company or any of its subsidiaries or controlled affiliates; or (c) solicit, induce or attempt to induce any potential customer, vendor, contractor, employee, consultant or advisor whose identity and potential relationship with the Company or any of its subsidiaries or controlled affiliates the Consultant learned as a result of my employment with the Company, not to establish, or to diminish or materially alter, such potential relationship with the Company or any of its subsidiaries or controlled affiliates. In the event that a court finds this Section 4.3, or any of its restrictions, to be unenforceable or invalid, the Consultant and the Company agree that (i) this Section 4.3 will be automatically modified to provide the Company with the maximum protection of its business interests allowed by law and (ii) the Consultant shall be bound, and such court shall enforce, this Section 4.3 as so modified.

ARTICLE 5. OWNERSHIP OF INVENTIONS

5.1. Definition. As used herein, "Inventions" shall mean all inventions, ideas, discoveries, developments, methods, data, information, improvements and biological or chemical materials, (whether or not protectable under state, federal, or foreign patent, copyright, trade secrecy or similar laws) conceived, reduced to practice or tangible medium, discovered or developed by the Consultant or under the Consultant's direction (whether alone or with others), whether or not or on the premises of the Company, which arise out of the Consultant's Services.

5.2. Disclosure of Inventions. The Consultant shall promptly disclose to the Company any and all Inventions and shall maintain adequate and current written records (in the form of notes, sketches, drawings or otherwise as may be specified by the Company) to document the conception, reduction to practice, discovery or development of any Invention. Such records shall be considered Confidential Information of the Company hereunder and shall be available to and remain the sole property of the Company at all times.

5.3. Assignment and Cooperation. The Consultant acknowledges and agrees that all Inventions shall be the sole property of the Company. The Consultant hereby assigns and, if relevant, shall cause all of the Consultant's employees, officers and directors to assign to the Company (or any other person or entity designated in writing by the Company) all of the Consultant's and the Consultant's representatives' right, title and interest in and to the Inventions and any and all related patent rights, copyrights, trademarks and other industrial and intellectual property rights and applications and registrations therefor anywhere in the world. During and after the Consultant's engagement with the Company, the Consultant and/or Consultant's employees, officers and directors, as relevant, shall cooperate with the Company or its designee, at the Company's request and expense, in obtaining proprietary protection for the Inventions, including executing all documents which the Company shall reasonably request in order to perfect the Company's rights in the Inventions. The Consultant hereby appoints the Company as the Consultant's attorney to execute and deliver any such documents on the Consultant's behalf in the event the Consultant should fail or refuse to do so within a reasonable period following the Company's request.

ARTICLE 6. CONFIDENTIAL INFORMATION AND MATERIALS

6.1. Definitions. As used herein, "Confidential Information" shall mean any scientific, technical, business, financial or other information of the Company or its affiliates that is treated by the Company as confidential or proprietary and that becomes known to or is developed by the Consultant in connection with the Consultant's engagement with the Company, regardless of whether such information is specifically labeled or identified as "Confidential" or prepared in full or in part by the Consultant and regardless of whether such information is in written, oral, electronic or other form. Confidential Information may include, without limitation, trade secrets, know-how, inventions, technical data or specifications, testing methods, business or financial information, research and development activities, product and marketing plans, and customer and supplier information. Any similar information obtained by or given to the Company about or belonging to its suppliers, licensors, licensees, partners, affiliates, customers, potential customers or others shall also be considered Confidential Information. As used herein, "Materials" shall mean any biological or chemical materials which may become known to the Consultant in connection with the Consultant's engagement with the Company and may include, without limitation, any and all reagents, substances, chemical compounds, subcellular constituents, cells or cell lines, organisms and progeny, mutants, derivatives or replications thereof or therefrom.

6.2. Exceptions. Confidential Information shall not include information which the Consultant can demonstrate:

(a) was in the public domain prior to the time of its disclosure under this Agreement;

(b) entered the public domain after the time of its disclosure under this Agreement through means other than an unauthorized disclosure resulting from an act or omission by the Consultant;

(c) was independently developed or discovered by the Consultant outside of the course of performing the Services prior to the time of its disclosure under this Agreement; or

(d) is or was disclosed to the Consultant at any time, whether prior to or after the time of its disclosure under this Agreement, by sources other than the Company and its affiliates having no duty of confidentiality, whether direct or indirect, with respect to such Confidential Information and having the legal right to disclose such Confidential Information.

Notwithstanding any other provision hereof, it shall not be a violation of this Agreement for the Consultant to disclose Confidential Information to the extent such disclosure is required to comply with applicable laws or governmental regulations, provided that the Consultant provides prior written notice of such disclosure to the Company and takes reasonable and lawful actions to avoid and/or minimize the extent of such disclosure.

6.3. Ownership; Consultant Obligations. The Consultant understands that the Company continually obtains and develops valuable Confidential Information and Materials. The Consultant acknowledges that the Consultant's relationship with the Company is one of high

trust and confidence and that in the course of the Consultant's engagement and prior period of employment with the Company, the Consultant has and will have access to and contact with Confidential Information and Materials. The Consultant acknowledges that the Company is and shall at all times remain the sole owner of the Confidential Information and Materials. With respect to all Confidential Information and Materials, the Consultant acknowledges and agrees:

(a) that all Confidential Information and all Materials, and all material or medium, including, without limitation, all files, letters, memoranda, reports, data, forms, manuals, sketches, laboratory notebooks, computer records or files, and other records and any other written, photographic, electronic or tangible material or medium, containing the Confidential Information or Materials prepared or compiled by the Consultant or furnished to or accessible by the Consultant in the course of Consultant's engagement or prior period of employment with the Company are and shall remain the exclusive property of the Company or the third party providing such Confidential Information or Materials to the Consultant or the Company;

(b) that the Consultant shall not publish, disclose or otherwise make available to any third party, any Confidential Information or Materials, except (i) to employees of the Company as required in connection with the performance of the Services, (ii) to third parties, such as clinical sites and contract research organizations, as reasonably required in connection with the performance of the Services, provided that such third parties and the Company have executed a confidential disclosure agreement pursuant to which such third parties have agreed to protect the confidentiality of such Confidential Information or (iii) as otherwise expressly authorized in writing by the Company;

(c) that the Consultant shall not use such Confidential Information or Materials for Consultant's own benefit, or for the benefit of any other person or business entity, or for any other purpose, except for the performance of the Services to the Company and in accordance with any Company policies given to the Consultant in writing with respect to the protection of such Confidential Information or Materials;

(d) that the Consultant shall use the Confidential Information and Materials in accordance with all applicable governmental laws, rules, and regulations; and

(e) that the Consultant will exercise all reasonable precautions to protect the integrity and confidentiality of Confidential Information and Materials in Consultant's possession and not to remove any material or medium containing Confidential Information or any Materials from the Company's premises except to the extent reasonably necessary to perform the Services.

Upon the termination of Consultant's engagement, or at any time upon the Company's request, the Consultant shall return immediately to the Company any and all material or medium containing any Confidential Information, or copies thereof, or Material then in Consultant's possession or under Consultant's control, provided, however, that the Consultant may retain one copy of such Confidential Information solely for the purpose of determining the extent of Consultant's obligations hereunder.

6.4. Trade Secrets; Whistleblower Protections. In accordance with 18 U.S.C. §1833, notwithstanding anything to the contrary in this Agreement or any other agreement between the Consultant and the Company or any of its subsidiaries (together, the "Subject Documents"): (a) the Consultant will not be in breach of any Subject Document, and shall not be held criminally or civilly liable under any federal or state trade secret law (i) for the disclosure of a trade secret that is made in confidence to a federal, state, or local government official or to an attorney solely for the purpose of reporting or investigating a suspected violation of law, or (ii) for the disclosure of a trade secret that is made in a complaint or other document filed in a lawsuit or other proceeding, if such filing is made under seal; and (b) if the Consultant files a lawsuit for retaliation by the Company for reporting a suspected violation of law, the Consultant may disclose the trade secret to the Consultant's attorney, and may use the trade secret information in the court proceeding, if the Consultant files any document containing the trade secret under seal, and does not disclose the trade secret, except pursuant to court order. Furthermore, the Parties agree that nothing in the Subject Documents prohibits the Consultant from reporting possible violations of federal law or regulation to any governmental agency or entity in accordance with the provisions of and rules promulgated under any whistleblower protection provisions of state or federal law or regulation or releases or restrains the Consultant's right to receive an award for information provided to any such government agencies or entities.

6.5. Return of Property. The Consultant affirms that the Consultant has returned to the Company all notes, memoranda, specifications, drawings, devices, formulas, and documents, together with all copies thereof, any other material containing or disclosing any Confidential Information or Materials and any other physical or personal property that is the property of the Company that the Consultant previously had in the Consultant's possession.

ARTICLE 7. TERM AND TERMINATION

7.1. Term. This Agreement shall commence on the Effective Date and shall remain in effect through the first anniversary of the Effective Date (such period, the "Consulting Period"), unless earlier terminated in accordance with the provisions of this Article 7. Notwithstanding the foregoing, unless the Release Effective Date occurs on or prior to October 10, 2021, the Consulting Period shall terminate immediately and the Consultant shall not be entitled to be paid any of the compensation pursuant to Article 2 above regardless of the provision of any Services prior to such date.

7.2. Termination by Either Party. Either Party may terminate this Agreement upon thirty (30) days' prior written notice, with or without cause. Notwithstanding the foregoing, the Company may terminate this Agreement immediately upon giving written notice of termination to the Consultant if the Consultant breaches or threatens to breach any provision of Articles 3, 4, 5 or 6. In addition, the Company may terminate this Agreement effective immediately upon written notice to the Consultant (or the Consultant's legal representative) in the event of death or legal incapacity of any designated the Consultant representative. Any termination for cause hereunder shall be without prejudice to any right or remedy the terminating Party may otherwise have under this Agreement.

7.3. Effect of Expiration or Termination. Upon expiration or termination of this Agreement, neither the Consultant nor the Company shall have any further obligations under this

Agreement, except for liabilities accrued through the date of termination (including amounts payable to the Consultant pursuant to Article 2 through the termination date) and Articles 4, 5, 6, and 10 and this Section 7.3 shall survive.

ARTICLE 8. GOOD STANDING AND DEBARMENT

8.1. Good Standing. The Consultant represents and warrants that the Consultant (i) shall comply with all federal, state and local laws, rules, regulations and ordinances, and all professional standards, applicable to the Services including, but not limited to, the Federal anti-kickback statute (21 U.S.C. § 1320a-7(a)); (ii) has a valid state medical or professional license and is currently in good standing; (iii) has not been subject to pending or final adverse action, suspension, revocation, termination, disciplinary action or other similar action by any healthcare licensing authority, medical board, medical society, medical association or accrediting body; and (iv) has not been charged, convicted, pleaded guilty or no contest of a criminal offense related to the provision of healthcare items or services, or is subject to any such pending action.

8.2. Debarment. The Consultant further represents and warrants that the Consultant: (i) has not been convicted of an offense related to any federal or state healthcare program including, but not limited to those within the scope of 42 U.S.C. § 1320a-7(a); (ii) is not currently excluded, debarred, suspended or otherwise ineligible to participate in federal or state health care programs, including, but not limited to debarment under Section 306 of the Federal Food Drug and Cosmetic Act (21 U.S.C. § 335(a)) or in Federal procurement or non-procurement programs by the Office of Inspector General or the General Services Administration; (iii) has not been excluded, suspended or is other ineligible for federal or state healthcare program participation, including but not limited to, persons identified on the General Services Administration's List of Parties Excluded from Federal Programs or the U.S. Department of any of the FDA Clinical Investigator enforcement lists, including but not limited to, the Disqualified/Totally Restricted List, Restricted List, or Adequate Assurances List. The Consultant immediately shall notify the Company if at any time during the term of this Agreement the Consultant becomes aware that the Consultant, or any person employed by Consultant, in connection with any work to be performed for or on behalf of Company, has become or is (i) in the process of being charged, convicted, excluded, debarred, suspended or otherwise rendered ineligible to participate in Federal healthcare programs or in Federal procurement or non-procurement programs by the Office of Inspector General or the General Services Administration; (ii) subject to disciplinary action by any healthcare licensing authority; (iii) subject to criminal charges related to the provision of healthcare items or services; or (iv) on an enforcement list. The Consultant agrees to promptly inform the Company in writing of any exclusion, suspension, conviction or other event that makes the Consultant, or any person employed by the Consultant, ineligible to participate during the terms of this Agreement in Federal healthcare programs or in Federal procurement or non-procurement programs, or if any action, suit, claim or investigation or proceeding relating to the foregoing is pending, or to the best of the Consultant's knowledge is threatened.

ARTICLE 9. RELEASE OF CLAIMS

9.1. Release of Claims. In consideration of the Company's agreement to enter into this Agreement, the Consultant, on the Consultant's own behalf and on behalf of any of the

Consultant's affiliated companies or entities and any of the Consultant's or their respective heirs, family members, executors, agents and assigns, hereby and forever releases the Company and any of its direct or indirect subsidiaries and affiliates, and any of its or their respective current and former officers, directors, equity holders, managers, employees, agents, investors, attorneys, shareholders, administrators, affiliates, benefit plans, plan administrators, insurers, trustees, divisions, and subsidiaries and predecessor and successor corporations and assigns (collectively, the "Releasees") from, and agrees not to sue concerning, or in any manner to institute, prosecute, or pursue, any disputes, claims, complaints, grievances, charges, actions, petitions, and demands (collectively, "Claims"), whether presently known or unknown, suspected or unsuspected, that the Consultant may possess against any of the Releasees arising from any omissions, acts, facts, or damages that have occurred up until and including the date the Consultant signs this Agreement, including, without limitation:

(a) any and all Claims relating to or arising from the Consultant's prior employment or service relationship with the Company or any of its direct or indirect subsidiaries or affiliates and the termination of that relationship;

(b) any and all Claims relating to, or arising from, the Consultant's right to purchase, or actual purchase of any shares of stock or other equity interests of the Company or any of its affiliates, including, without limitation, any Claims for fraud, misrepresentation, breach of fiduciary duty, breach of duty under applicable state corporate law, and securities fraud under any state or federal law;

(c) any and all Claims for wrongful discharge of employment; termination in violation of public policy; discrimination; harassment; retaliation; breach of contract, both express and implied; breach of covenant of good faith and fair dealing, both express and implied; promissory estoppel; negligent or intentional infliction of emotional distress; fraud; negligent or intentional misrepresentation; negligent or intentional interference with contract or prospective economic advantage; unfair business practices; defamation; libel; slander; negligence; personal injury; assault; battery; invasion of privacy; false imprisonment; conversion; and disability benefits;

(d) any and all Claims for violation of any federal, state, or municipal statute, including, but not limited to, Title VII of the Civil Rights Act of 1964; the Civil Rights Act of 1991; the Rehabilitation Act of 1973; the Americans with Disabilities Act of 1990; the Equal Pay Act; the Fair Credit Reporting Act; the Age Discrimination in Employment Act of 1967 (the "ADEA"); the Older Workers Benefit Protection Act; the Employee Retirement Income Security Act of 1974; the Worker Adjustment and Retraining Notification Act; the Family and Medical Leave Act; the Sarbanes-Oxley Act of 2002; and the Massachusetts Fair Employment Practices Act;

(e) any and all Claims for violation of the federal or any state constitution;

(f) any and all Claims arising out of any other laws and regulations relating to employment or employment discrimination;

(g) any Claim for any loss, cost, damage, or expense arising out of any dispute over the non-withholding or other tax treatment of any of the proceeds received by the Consultant as a result of this Agreement;

(h) any and all Claims arising out of the wage and hour and wage payment laws and regulations of the state or states in which the Consultant has provided service to the Company or any of its affiliates, including without limitation the Massachusetts Payment of Wages Law; and

(i) any and all Claims for attorneys' fees and costs.

The Consultant agrees that the release set forth in this Section shall be and remain in effect in all respects as a complete general release as to the matters released. This release does not release (i) the Consultant's right to report possible violations of federal law or regulation to any governmental agency or entity in accordance with the provisions of and rules promulgated under any whistleblower protection provisions of state or federal law or regulation (including the Consultant's right to receive an award for information provided to any such government agencies or entities), (ii) the Consultant's right to file a charge with or participate in a charge, investigation or proceeding by the Equal Employment Opportunity Commission, or any other local, state, or federal administrative body or government agency that is authorized to enforce or administer laws related to employment, against the Company (with the understanding that the Consultant's release of claims herein bars the Consultant from recovering monetary or other individual relief from the Company or any Releasee in connection with any charge, investigation or proceeding, or any related complaint or lawsuit, filed by the Consultant or by anyone else on the Consultant's behalf before the federal Equal Employment Opportunity Commission or a comparable state or local agency), (iii) Claims for any state unemployment insurance benefits or disability insurance benefits pursuant to the terms of applicable state law, (iv) Claims to continued participation in certain of the Company's group benefit plans pursuant to the terms and conditions of Consolidated Omnibus Budget Reconciliation Act of 1985, (v) any other Claims that cannot be released by private agreement under applicable law, but only to the extent such Claims cannot be released under such law, (vi) Claims under this Agreement and (vii) Claims for indemnification by the Company pursuant to contract, directors' and officers' insurance, the Company's amended and restated certificate of incorporation or amended and restated bylaws or applicable law.

9.2. Acknowledgment of Waiver of Claims under ADEA. The Consultant understands and acknowledges that the Consultant is waiving and releasing any rights the Consultant may have under the ADEA, and that this waiver and release is knowing and voluntary. The Consultant understands and agrees that this waiver and release does not apply to any rights or Claims that may arise under the ADEA after the date the Consultant signs this Agreement. The Consultant understands and acknowledges that the consideration given for this waiver and release is in addition to anything of value to which the Consultant was already entitled. The Consultant further understands and acknowledges that the Consultant has been advised by this writing that: (a) the Consultant should consult with an attorney prior to executing this Agreement; (b) the Consultant has 21 days within which to consider this Agreement, and the Parties expressly agree that such time period to review this Agreement shall not be extended upon any material or immaterial changes to this Agreement; (c) the Consultant has seven

business days following the Consultant's execution of this Agreement to revoke this Agreement by delivering written notice to the General Counsel of the Company; (d) this Agreement shall not be effective until after the revocation period has expired (such effective date, the "Release Effective Date"); and (e) nothing in this Agreement prevents or precludes the Consultant from challenging or seeking a determination in good faith of the validity of this waiver under the ADEA, nor does it impose any condition precedent, penalties, or costs for doing so, unless specifically authorized by federal law. In the event the Consultant signs this Agreement and returns it to the Company in less than the 21-day period identified above, the Consultant hereby acknowledges that the Consultant has freely and voluntarily chosen to waive the time period allotted for considering this Agreement.

ARTICLE 10. MISCELLANEOUS

10.1. Indemnification. The Company agrees to defend, indemnify and hold harmless the Consultant from any third party actions, suits, claims, demands, prosecutions, liabilities and fines (including reasonable attorneys' fees) (collectively, "Claims") arising directly out of or in connection with this Agreement, provided however, that this indemnification shall not extend to any Claims arising as a direct result of any breach of any representation or warranty made by the Consultant or its representatives hereunder or any negligence or intentional wrongful acts or omissions on the part of the Consultant or its representatives. The foregoing indemnification shall be contingent upon the Consultant providing the Company with prompt written notice of such Claims and sole authority to defend and/or settle any such Claims. Notwithstanding the foregoing, the Company shall not settle any Claim which would result in an admission of liability on the part of the Consultant without the Consultant's prior written consent.

10.2. Independent Contractor. The Consultant is an independent contractor under this Agreement. The Consultant is not any employee or agent of the Company and as a result will not be entitled to participate in, or receive any benefit, coverage, privilege or right as an employee, including without limitation, social security, unemployment, medical, pension, or under any employee benefit or welfare plan of the Company nor have authority to represent or bind the Company in any manner in dealings with third parties. The Consultant shall have sole responsibility for payment of all federal, state and local taxes or contributions imposed or required under unemployment insurance, social security and income tax laws and for filing all required tax forms with respect to any amounts paid by the Company to the Consultant for the Services hereunder. The Consultant confirms and acknowledges that the Consultant has read and understands the Company's Insider Trading Policy and agrees to comply with the requirements and obligations applicable to the Consultant thereunder.

10.3. Non-Referral. The Parties agree that the Consultant is under no obligation to solicit, refer or solicit referrals of patients for any Company business. The Consultant will not receive any benefit of any kind for making any referrals nor suffer any detriment for not making such referrals. The Parties further agree that no amount paid hereunder is intended to be, nor shall be construed as, an inducement or payment for referral of or recommending referral of patients for any Company business by the Consultant to Company (or its affiliates) or by Company (or its affiliates) to the Consultant. In addition, the fees charged hereunder do not include any discount, rebate, kickback or other reduction in charge, and the fees charged hereunder are not intended to be, nor shall they be construed as, an inducement or payment for

referral, or recommendation of referral, of business by the Consultant to Company (or its affiliates) or by Company (or its affiliates) to the Consultant. The sole purpose of the fee paid to the Consultant hereunder is to pay fair market value for the time and effort the Consultant will spend.

10.4. Anti-Bribery Laws. Consultant shall comply with the requirements of all applicable anti-bribery legislation both national and foreign, including but not limited to the U.S. Foreign Corrupt Practices Act and the U.K. Bribery Act Consultant ("Anti-Bribery Laws"), and Consultant has not and will not make, promise or offer to make any payment or transfer anything of value (directly or indirectly) to (a) any individual, (b) corporation, (c) association, (d) partnership, or (e) public body (including but not limited to any officer or employee of any of the foregoing) who, acting in their official capacity or of their own accord, are in a position to influence, secure or retain any business for (and/or provide any financial or other advantage to) Company by improperly performing a function of a public nature or a business activity with the purpose or effect of public or commercial bribery, acceptance of or acquiescence in extortion, kickbacks or other unlawful or improper means of obtaining or retaining business.

10.5. Notices. All notices to be given pursuant to this Agreement shall be in writing and shall be deemed to have been duly given to a Party (a) upon delivery if delivered by hand, (b) five business days after mailed by registered or certified mail, return receipt requested, postage prepaid, or (c) one business day after mailing via any reputable overnight delivery service, postage prepaid and with delivery confirmation, in each case to such Party at its address set forth herein or at such other address as such Party shall have designated by notice in writing to the other Party.

10.6. Severability. If any one or more of the provisions of this Agreement shall, for any reason, be held to be invalid, illegal or unenforceable in any respect, such invalidity, illegality or unenforceability shall not affect any other term or provision of this Agreement, and all other provisions shall remain in full force and effect. If any provision in this Agreement shall be held to be excessively broad, it shall be construed by limiting it so as to be enforceable to the extent compatible with applicable law.

10.7. Captions. Captions of Articles and Sections of this Agreement have been added only for convenience, shall not be deemed to be a part of this Agreement, and shall not be admissible for the purpose of proving the intent of the Parties.

10.8. Complete Agreement; Amendments. This Agreement, including any Schedules hereto, constitutes the entire agreement between the Parties with respect to the subject matter hereof and supersedes all prior agreements with respect to the subject matter of this Agreement. This Agreement may not be modified or amended except in a writing signed by both Parties. Industry regulations or other considerations may require that Company update this Agreement from time to time. In such cases, the Consultant will receive a new Consulting Agreement to review and sign, which will supersede and replace the existing Agreement.

10.9. Rights of Publicity. Neither Party shall have the right to use the other Party's name or likeness in any publications, publicity or other materials or presentations without obtaining the prior written consent of other Party.

10.10. Applicable Law. This Agreement shall be considered to have been made in the United States, and shall be interpreted in accordance with the laws of the Commonwealth of Massachusetts, United States of America, without regard to its conflicts of laws principles.

10.11. Nonwaiver Provision. The waiver by either Party hereto of any right hereunder or of the failure to perform or of a breach by the other Party shall not be deemed a waiver of any other right hereunder or of any other breach or failure by said other Party whether of a similar nature or otherwise.

10.12. Assignment. Neither this Agreement nor any rights or obligations hereunder shall be assignable by either Party hereto without the prior written consent of the other Party, except that the Company may assign this Agreement to a subsidiary or affiliate or in connection with the merger, consolidation or sale of all or substantially all of its business or assets to which the Services relate.

10.13. Counterparts. This Agreement may be executed in one or more counterparts, each of which shall be deemed an original and all of which together shall be deemed to be one and the same instrument.

10.14. Legal and Equitable Relief. The Parties acknowledge and agree that the restrictions contained in Articles 3, 4, 5, and 6 of this Agreement are necessary for the protection of the business and goodwill of the Company and are reasonable for such purpose. The Consultant acknowledges and agrees that any breach of any of the foregoing such provisions by the Consultant may cause substantial and irreparable injury to the Company; such injury may be difficult to measure; and monetary damages, even if ascertainable, may be inadequate compensation for such injury. Therefore, in the event of any breach by the Consultant of any such provision, the Company shall be entitled (in addition to monetary damages and to any other remedies available to the Company under this Agreement and at law) to seek equitable relief, including injunctive relief.

10.15. Transparency Reporting Requirements. The Consultant acknowledges that applicable Federal and State disclosure and reporting laws, regulations and industry guidelines may require Company to collect and report to government agencies any direct or indirect payment or transfer of value it makes to certain healthcare providers and organizations (collectively "Financial Transparency Laws"), which include without limitation, relevant provisions of the Affordable Care Act of 2010 and its implementing regulations. Notwithstanding anything to the contrary herein, Company may disclose, without prior notification to the Consultant, any information relating to this Agreement that Company reasonably believes is necessary to comply with Financial Transparency Laws and that this information may be posted on governmental websites or otherwise made publicly available. The Consultant shall cooperate with Company in its compliance with Financial Transparency Laws in connection with this Agreement and consents and agrees to Company's disclosure of all payments and transfers of value received by the Consultant from Company. The Consultant shall promptly provide Company, in the format Company requests, with any information that Company reasonably believes it needs to comply with Financial Transparency Laws in connection with this Agreement. Without limiting the generality of the foregoing, such information may include information that relates to any Third Party healthcare provider and/or

organization that receives any direct or indirect payment or other transfer of value from or on behalf of the Consultant in connection with this Agreement where Company reasonably believes that such payment and/or transfer of value must be reported under Financial Transparency Laws.

IN WITNESS WHEREOF, the Company and the Consultant have duly executed and delivered this Agreement as of the date first written above.

RHYTHM PHARMACEUTICALS, INC.	CONSULTANT:
By:	By:
Name: David Meeker	Name: Murray Stewart, D.M., F.R.C.P.
Title: President and Chief Executive Officer	
Date:	Date:

SCHEDULE A

Equity Awards

Grant Date	Award Type	Exercise Price	Vested Shares*	Shares Eligible to Vest**
10/15/2018	Option	$26.54	68,750	0
2/13/2019	Option	$29.78	37,500	0
2/14/2020	Option	$17.87	33,000	0
6/30/2020	RSU	N/A	0	25,000
2/11/2021	Option	$30.66	7,031	0
2/11/2021	RSU	N/A	0	2,344

* Represents the number of shares of the Company's common stock as to which the Equity Award was vested as of the Separation Date.

** Represents the maximum number of shares of the Company's common stock as to which the Equity Award will be eligible to vest during the term of the Agreement in accordance with its original vesting schedule, subject to the terms of the Agreement and the Consultant's continued Services through the applicable vesting date(s).

Exhibit 21.1

Subsidiaries of Rhythm Pharmaceuticals, Inc.

Entity	Jurisdiction of Organization or Incorporation
Rhythm Pharmaceuticals Limited	Ireland
Rhythm Securities Corp.	Massachusetts
Rhythm Pharmaceuticals Netherlands, B.V.	The Netherlands
Rhythm Pharmaceuticals UK Limited	United Kingdom
Rhythm Pharmaceuticals France SAS	France
Rhythm Pharmaceuticals Italy S.r.L.	Italy
Rhythm Pharmaceuticals Canada Inc.	Canada

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. 333-260689) of Rhythm Pharmaceuticals, Inc.,

(2) Registration Statement (Form S-8 No. 333-253709) pertaining to the 2017 Equity Incentive Plan of Rhythm Pharmaceuticals, Inc.,

(3) 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.,

(4) 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.,

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

(6) 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, 2022, 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, 2021.

/s/ Ernst & Young LLP

Boston, Massachusetts
March 1, 2022

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, 2022

/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, 2022

/s/ Hunter C. Smith
Name: Hunter C. Smith
Title: Chief Financial Officer
(Principal Financial 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, 2021 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, 2022

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, 2021 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 Officer)

March 1, 2022