2021 ANNUAL REPORT

Rhythm® PHARMACEUTICALS

"My weight is my biggest challenge, and it affects every aspect of my daily activities. When I'm hungry, I can't stop it because I don't have the signal from my stomach to my brain."

Izzy, *who was diagnosed with Bardet-Biedl syndrome when she was 5 years old.*

Rhythm is a global, commercial-stage biopharmaceutical company focused on transforming the care of patients living with early-onset, severe obesity and hyperphagia, a pathological and insatiable hunger, driven by genetic or acquired impairments of the melanocortin-4 receptor (MC4R) pathway.

The MC4R pathway is a key hypothalamic pathway that regulates hunger, caloric intake, and energy expenditure, consequently affecting body weight. Rhythm is developing setmelanotide, an MC4R agonist designed to selectively target the MC4R pathway. It has shown the potential to restore the function impaired by genetic variants, the root cause of hyperphagia and obesity.

Under the brand name IMCIVREE, setmelanotide was approved in the United States in 2020 and authorized by the European Commission and Great Britain's MHRA in 2021, making it the first-ever treatment for certain rare genetic diseases of obesity, namely POMC, PCSK1 or LEPR deficiency obesities. Rhythm also is seeking regulatory approvals to expand IMCIVREE's indications to include Bardet-Biedl syndrome (BBS) and potentially Alström syndrome.

In addition, Rhythm is advancing a broad clinical development program. We have initiated phase 2 and 3 trials evaluating setmelanotide – a daily subcutaneous injection - for the treatment of obesity due to a deficiency in one or more of many additional genes associated with the MC4R pathway. We also are developing a weekly formulation of setmelanotide.

Rhythm's clinical strategy is fueled by a genetic database - the largest known obesity DNA database - with approximately 45,000 sequencing samples – designed to improve the understanding, diagnosis, and care of patients with severe obesity due to certain genetic deficiencies.

A Message to Our Stockholders

At Rhythm, our commitment to people with rare genetic diseases of obesity extends beyond the development of potential medicines – we embrace a responsibility to engage with and listen to each member of the community to help bolster both the individual and collective understanding of rare genetic diseases of obesity and drive positive change. On the cover of this, our 2021 annual report, are Leigh and her daughter Izzy. Izzy was diagnosed with Bardet Biedl syndrome (BBS) when she was about 5 years old, after seeing 15 doctors in six different states. Even in the absence of a specific therapy, receiving a concrete diagnosis can provide a rare disease patient and their family some relief in the knowledge of what is ahead. While patients suffering from a rare disease may share some common challenges, each experience, each journey is unique. The courage shown by patients like Izzy and their families as they undergo their journey inspires us at Rhythm to first understand that journey, and then work to lessen the burdens that a life with a rare disease presents. We are tackling the challenges each of these patients and their families share, while not losing sight of the unique and highly personal nature of each person's story.

Our challenge is to ensure that patients like Izzy can reliably see an expert who considers the full range of possibilities. This starts with education, creating a level of awareness such that when a physician hears Izzy's story, he or she will recognize BBS as a possible diagnosis. It may not be the first physician they see, but it certainly should not be the fifteenth. Beyond the struggles we face in a lack of awareness, specific testing required to diagnose a rare disease may not be available for patients, or worse – not yet invented. In addition to driving broader awareness, Rhythm provides a comprehensive gene panel that may inform the diagnosis of a rare genetic disease of obesity or support the clinical diagnosis, as is the case with BBS. The availability of a test can change the diagnostic journey dramatically. A health care provider need not know which disease they are testing for, but rather in the case of a patient presenting with a history of early-onset, severe obesity and hyperphagia, a severe pathologic form of hunger, they simply need to consider the underlying genetics. The panel results can inform a diagnosis and put a patient on a better, swifter track to finding potential treatment options.

> *"We know that each patient and family living with a rare genetic disease obesity is unique."*

On one hand, we work with the health care system to improve its ability to care for patients like Izzy. On the other hand, we are committed to understanding their individual stories. Patients with genetic causes of early-onset, severe obesity and hyperphagia face not only the physical challenges posed by a feeling of constant hunger, their obesity and its associated comorbidities, but they also face the severe emotional toll of dealing with social stigma and potentially biased opinions of family members, friends, teachers or colleagues. Each person's experience and needs are different, and it is our job at Rhythm to understand those differences and

provide appropriate individualized support. With our patient support services program – Rhythm InTune – we utilize our resources and ability to connect with individual patients and families to understand, learn, and adapt to their unique situation. Through these personalized connections, we strive to make a positive and visible impact on the community.

> *"Not all obesity is the same. Not every patient is the same. And not every health care system is the same."*

This desire and ability to understand what each patient and family values in their daily lives, from their community and from their health care teams, is foundational to achieving our mission. At Rhythm, our experienced team is eminently capable of reaching this level of understanding, and we are continuously humbled by the opportunity to do so. As we get to know the BBS community, we grow more confident in our ability to successfully meet their needs.

The confidence I have in the Rhythm team transcends our commitment to the BBS community, as we are focused on extending our reach to a series of MC4R pathway diseases – genetic, syndromic, or acquired. We are building a passionate, driven, and forward-thinking company one gene, one patient, and one employee at a time. In the last year alone, we've grown our employee count by 50 percent, increased our clinical development network and pipeline of trials, and extended our reach to a global level – and all this comes despite the challenges of COVID-19 and geopolitical tensions.

People are life-long learners, and organizations are no different. Like people, organizations grow as they learn. As we learn from our ever-growing patient community, we understand more about the MC4R pathway, setmelanotide's ability to address genetic or acquired impairments to pathway function, and the potential needs of a larger group of patients than any of us expected. We believe we are now better positioned than ever before to meet the needs of thousands, and potentially tens of thousands, of patients because we started small – with tens of patients. And grew.

The problem we are solving – the early-onset, severe obesity, the insatiable hyperphagia and all the co-morbidities and social stigmas that come with these rare genetic diseases of obesity – is global. We know full well that the individual patient and family needs in North America, Europe, the Middle East and China are unique, as are the health care systems within each country. Just as Rhythm is focused on addressing this class of diseases globally, our international organization concentrates on meeting the individual patient needs within their state or country's unique health care system. With our partners at RareStone, we are advancing the first opportunity to learn about – and address – the needs of rare genetic diseases of obesity in China.

We seek to transform the lives of patients suffering from hyperphagia and obesity due to an impaired MC4R pathway. This starts with an earlier diagnosis, and we look forward to the better outcomes that the right treatment will provide. We recognize that not all obesity is the same, that healthcare systems differ and, most importantly, that each patient and their needs are unique. We have a precise focus on supporting each patient with impairment in the MC4 pathway and their family with an understanding of their genetics and a growing sense of confidence that setmelanotide can help.

Sincerely,

David Meeker, MD
Chairman, President and
Chief Executive Officer

Clinical Programs Designed to Understand New Potential Indications

Setmelanotide is an MC4R agonist selectively targeting the MC4R pathway in the hypothalamus, which suggests the potential to restore the function impaired by genetic variants, a root cause of hyperphagia and obesity in these individuals. Under the brand name IMCIVREE, setmelanotide was approved in the United States in 2020 and authorized by the European Commission and Great Britain's MHRA in 2021 for treatment of certain rare genetic disorders of obesity.

	Patient Population	Phase 2	Phase 3	Regulatory Submission
IMCIVREE™ (setmelanotide) injection	POMC, PCSK1 or LEPR deficiency			US, EU, Great Britain
Setmelanotide *daily formulation*	Bardet-Biedl syndrome (BBS) or Alström syndrome			PDUFA target date: June 16, 2022; Type II Variation submitted to EMA
	Pediatrics (age 2 to <6 years); biallelic POMC, PCSK1 or LEPR deficiency or BBS			
	Heterozygous POMC/PCSK1/LEPR SRC1, SH2B1		Emanate Obesity and Hunger Clinical Trial	
	Additional genes with very strong MC4R pathway relevance	Daybreak Obesity and Hunger Clinical Trial		
	Hypothalamic obesity			
Setmelanotide *weekly formulation*	Biallelic or heterozygous POMC, PCSK1 or LEPR deficiency or BBS		Switch Study	
	BBS		*De novo* Study	

Study complete · Study underway · Planned study

Commitment to building, educating and supporting a community of health care providers who understand rare genetic diseases of obesity

Rhythm Delivers Multiple Presentations at Major Medical Conferences

In 2021, Rhythm collaborated with our trial investigators and key opinion leaders in making significant contributions to advance the scientific and medical understanding of hyperphagia and early-onset, severe obesity associated with rare genetic diseases of obesity and the need for genetic testing in these patient populations.

40 presentations

5 symposia

10 congresses

With continued evidence generation and ongoing research on disease burden and understanding, we expect to have many additional posters, presentations and publications in 2022.

Largest-known Genetic Database for Obesity

>45,000 sequencing samples from individuals with severe obesity

Rhythm has built what we believe to be the largest known DNA database, designed to improve the understanding, diagnosis and care of people living with severe obesity due to certain variants in genes associated with the MC4R pathway.

13,029 **sequencing samples from URO submissions***

2,758 **participating U.S. health care providers***

10,000 **additional URO test submissions anticipated in 2022**

UNCOVERING **RARE OBESITY®**

As Rhythm engages with health care providers across the United States and provides access to URO, our sponsored genetic testing panel, we are able to engage with and educate physicians in the community setting on the genetics of obesity and the MC4R pathway. URO is a tool that may be able to help them deliver care to their patients.

* As of December 31, 2021.

Peer-to-peer Health Care Provider Education and Engagement

GOLD Academy™
Genetic Obesity Learning Development

Rhythm's Genetic Obesity Learning Development (GOLD) Academy brings together health care providers to learn about rare genetic causes of obesity and the role of the melanocortin-4 receptor pathway in regulating hunger, caloric intake, energy expenditure, and consequently body weight. GOLD Academy programs, U.S. based non-CME programs sponsored by Rhythm, are physician-led, interactive presentations. GOLD Academy programs are web-based, in-person or hybrid.

23 **GOLD Academy programs held in 2021**

25 **anticipated in 2022**

1461 ***U.S. healthcare providers including endocrinologists, pediatricians, obesity specialists, bariatric surgeons, nurse practitioners, internists and more have participated since GOLD Academy launched in 2019.***

In addition to the GOLD Academy, in 2022 we are introducing the new Rare Genetic Diseases of Obesity (RGDO) Program with sessions in select community hospitals that focus on identifying, diagnosing and caring for adult patients or pediatric patients.

35 RGDO sessions planned in 2022

Focused BBS Education for Health Care Providers

Rhythm continues to add educational resources and expand the network of health care professionals who understand hyperphagia and early-onset, severe obesity associated with rare genetic diseases obesity, with a specific focus on Bardet-Biedl syndrome.

Educate on the MC4R pathway, a root cause of obesity and hyperphagia in BBS

Highlight the impacts of hyperphagia and obesity in BBS and overall health

Support identification of BBS patients through education on clinical diagnosis

PLANNED MARKETING AND DISEASE EDUCATION EFFORTS IN 2022:

15+ physicians expected in our speaker bureaus

30 live webinars (plus on demand)

Presence at **7** key medical and professional society congresses

Putting Patients at the Center of our Community

BBS Patient/Caregiver Speaker Programs Provide Meaningful Education for the Community

Our BBS Disease Education Webinars feature physicians as well as individuals living with BBS and caregivers to provide relevant and meaningful education. We focus on BBS and its symptoms, managing intense, hard-to-control hunger and obesity, personal experiences and more.

6 patient/caregiver speakers ***8 programs in early 2022*** ***82+ registrants***

Rhythm InTune Provides Personalized Support for Patients and Families

Individuals living with rare genetic diseases of obesity may face challenges in understanding their disease and treatment options. Rhythm InTune is a patient support program designed to help overcome these challenges, empowering patients and caregivers to achieve access to resources and potential treatment.

Rhythm InTune provides education and resources tailored to fit the unique needs of individuals living with rare genetic diseases of obesity, including BBS, Alström syndrome and obesity due to POMC, PCSK1 or LEPR deficiency. We match patients and caregivers with a dedicated patient education manager as a single point of contact for a personalized experience.

Education
offering resources to guide patients at every step

Connection
sharing opportunities to learn from the experience of others

Treatment support
assisting patients and providers to determine insurance coverage to get started and remain on treatment, providing financial assistance to eligible patients

Rhythm is a Global Company

and we are building out our presence with the same commitment to community building and education for patients, families and health care providers in several countries, including:

Denmark
Finland
France
Germany
Ireland
Italy
The Netherlands
Norway
Spain
Sweden
United Kingdom
Canada
Argentina
Israel
China

COMING SOON:
Children's Book on BBS

In collaboration with caregivers of individuals living with BBS, we are publishing an educational storybook for children and adolescents living with BBS. The story features a boy living with BBS named Gabe. Gabe's story is intended to help children living with BBS make sense of their feelings, provide education on why they are experiencing intense, hard-to-control hunger, and recognize they are not alone.

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

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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K, or this Annual Report, contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, and is subject to the "safe harbor" created by those sections. Any statements about our expectations, beliefs, plans, objectives, assumptions or future events or performance are not historical facts and may be forward-looking. Some of the forward-looking statements can be identified by the use of forward-looking terms such as "anticipates," "believes," "could," "estimates," "expects," "intends," "may," "might," "likely," "plans," "potential," "predicts," "projects," "seeks," "should," "target," "will," "would," or similar expressions and the negatives of those terms include forward-looking statements that involve risks and uncertainties. Forward-looking statements include, but are not limited to, statements regarding 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.

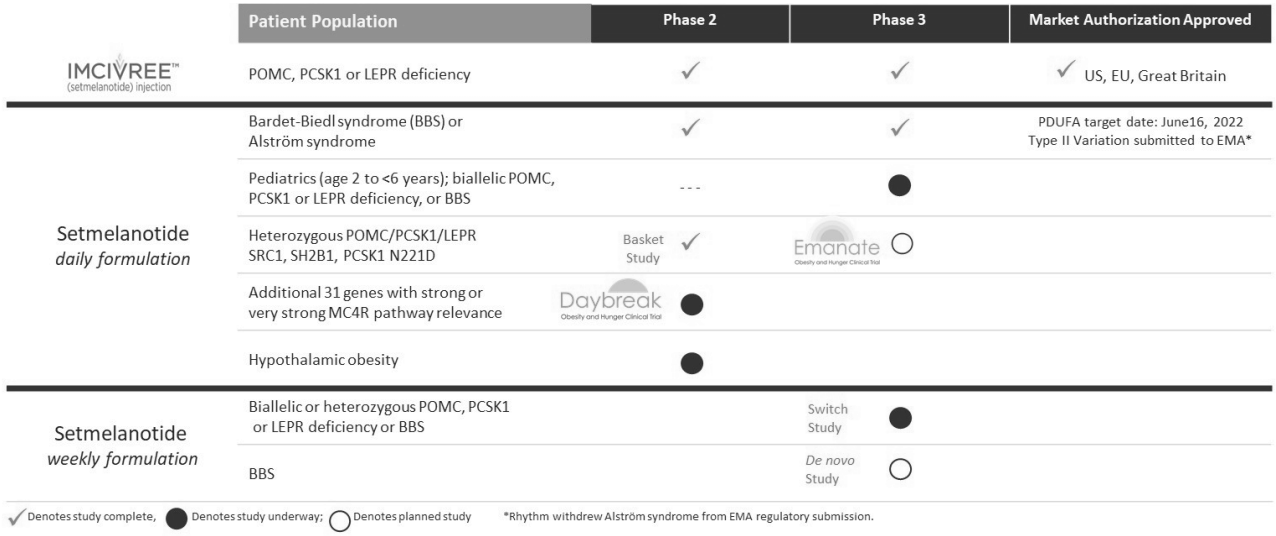
- **Ensure global access to IMCIVREE:** We are actively pursuing a global strategy for our clinical development, commercial and community building programs. In 2021, we laid the foundation for an emerging global organization focused on North America and major markets in Europe. We have established initial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

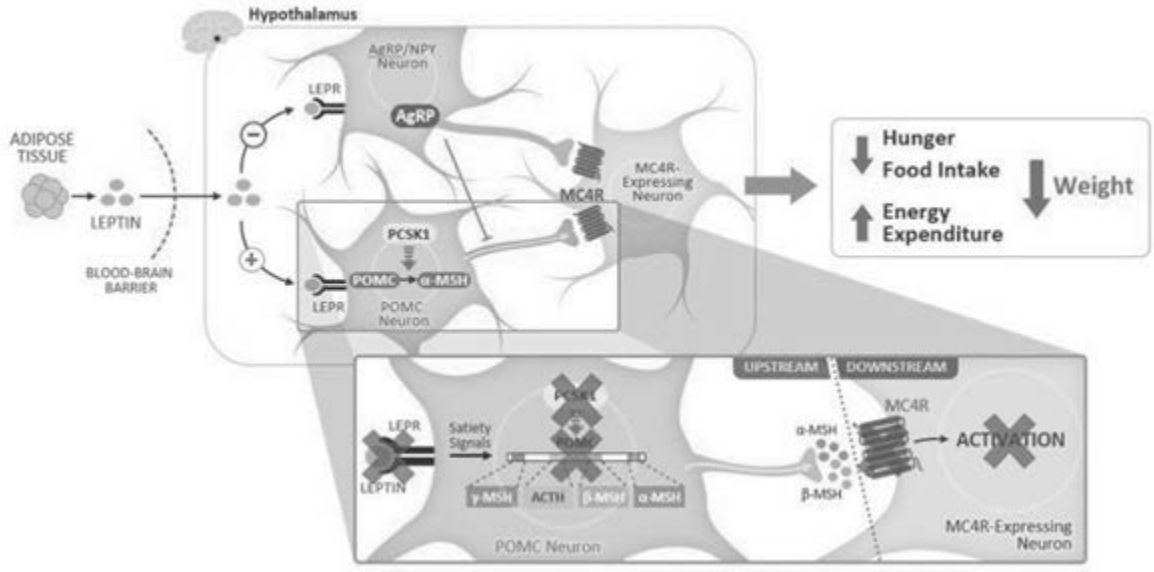
The MC4R pathway, which has been the focus of extensive scientific investigation for many years, regulates hunger, caloric intake, and energy expenditure, which consequently affect body weight. The critical role of the MC4R pathway in weight regulation is supported by the observation that single gene 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

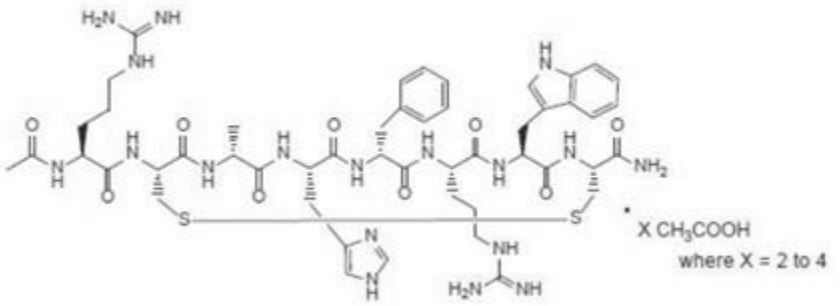
Although drugs approved for general obesity potentially can be used in patients with obesity and MC4R pathway variants, all currently available products have limited efficacy and treat symptoms without addressing the underlying biology of MC4R impairment. For example, drugs which delay gastric emptying 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) ≥ 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/m2) 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/m2) 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.

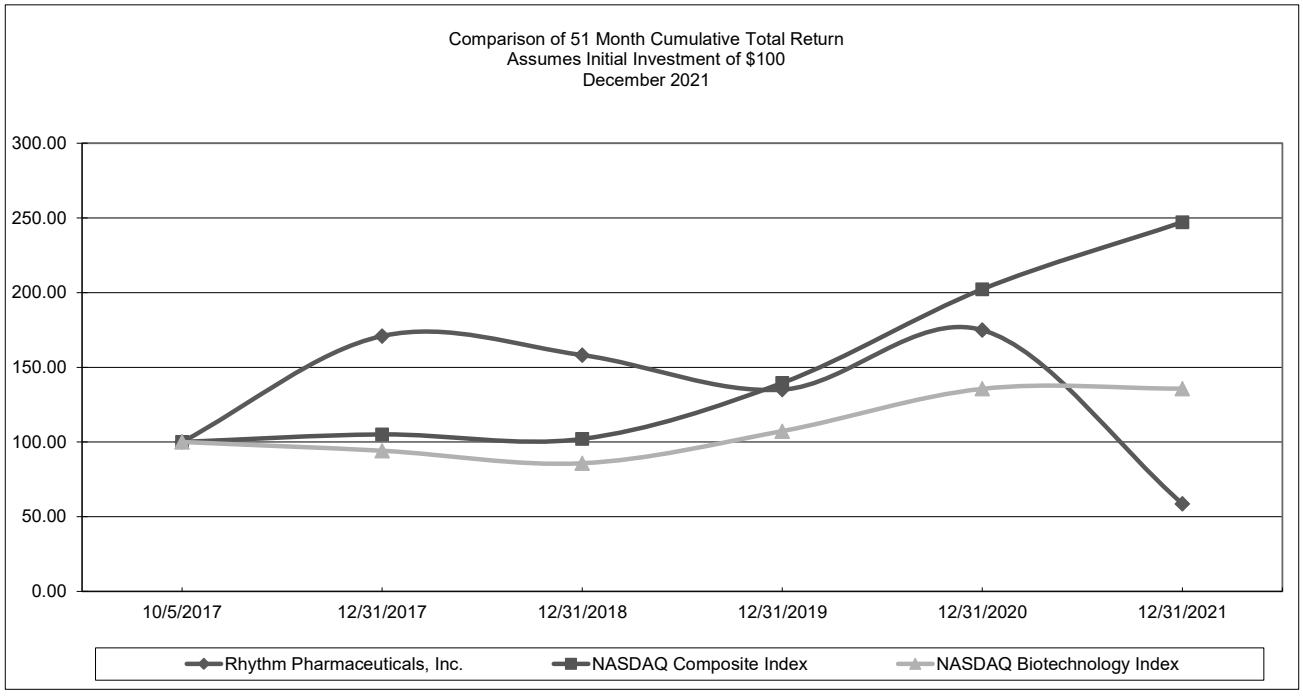
Dividend Policy

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

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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

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

Senior Management

David Meeker, MD

Chairman, President and Chief Executive Officer

Jennifer Chien

Executive Vice President, Head of North America

Yann Mazabraud

Executive Vice President, Head of International

Hunter Smith

Chief Financial Officer

Linda Shapiro

Chief Medical Officer

Joe Shulman

Chief Technical Officer

Pam Cramer

Chief Human Resources Officer

Elisabeth Crönert-Bendell

Senior Vice President, Head of Strategy

Jim Flaherty

Senior Vice President and General Counsel

Patrick Kleyn

Senior Vice President, Head of Translational Research and Development (TRAD)

Board of Directors

David Meeker, MD
Chairman

Ed Mathers
Lead Independent Director
Partner
New Enterprise Associates

Stuart Arbuckle
Executive Vice President and Chief Operating Officer
Vertex Pharmaceuticals

Camille L. Bedrosian, MD
Executive Vice President and Chief Medical Officer
Ultragenyx Pharmaceutical

Jennifer Good
President and Chief Executive Officer
Trevi Therapeutics, Inc.

Christophe R. Jean
Strategic Advisor
Oraxys S.A.

David McGirr
Former Senior Vice President and Chief Financial Officer
Cubist Pharmaceuticals, Inc.

Lynn Tetrault, JD
Former Executive Vice President of Human Resources and Corporate Affairs
Astra Zeneca, PLC

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Cautionary Note Regarding Forward-Looking Statements

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, and if needed, our marketing, commercial sales, and revenue generation, expectations surrounding our manufacturing arrangements, and the impact of the COVID-19 pandemic on our business and operations and our future financial results. 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.

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