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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

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

For the fiscal year ended December 31, 2022
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. ☐

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements. ☐
Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to § 240.10D-1(b). ☐
Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒.

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant was approximately $188.4 million, based on the closing price of the registrant's Common Stock on June 30, 2022, 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 56,747,577 shares of the registrant's Common Stock outstanding as of February 22, 2023.

DOCUMENTS INCORPORATED BY REFERENCE

The registrant intends to file a definitive proxy statement for the registrant's 2023 Annual Meeting of Stockholders within 120 days of the end of the fiscal year ended December 31, 2022. 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, 2022

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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 relationship with third-parties, our marketing, commercial sales, and revenue generation, expectations surrounding our manufacturing arrangements, the potential financial impact, growth prospects and benefits of our acquisition of Xinvento B.V., the impact of the COVID-19 pandemic and the current economic slowdown 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.

- Our Revenue Interest Financing Agreement with Healthcare Royalty Partners, and our other agreements, could restrict our ability to commercialize IMCIVREE, limit cash flow available for our operations and expose us to risks that could adversely affect our business, financial condition and results of operations.

- 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 and, guidance in the United States or abroad, 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.

- We may fail to realize the anticipated benefits of our acquisition of Xinvento B.V., those benefits may take longer to realize than expected, and we may encounter significant integration difficulties.

- If the third parties we rely on, and will continue to rely on, do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain additional regulatory approvals for or continue to commercialize setmelanotide and our business could be substantially hard.

- 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.

- Global events, such as the COVID-19 pandemic and the economic slowdown, have and may continue to adversely impact our business, including our preclinical studies, clinical trials and other commercialization prospects.

PART I

Item 1. Business

Overview

We are a global, commercial-stage biopharmaceutical company dedicated to transforming the lives of patients and their families living with rare diseases. We are focused on advancing our lead asset, IMCIVREE® (setmelanotide), as a precision medicine designed to treat hyperphagia and severe obesity caused by rare melanocortin-4 receptor (MC4R) pathway diseases. While obesity affects hundreds of millions of people worldwide, we are advancing IMCIVREE® (setmelanotide) for a subset of individuals who have hyperphagia, a pathological hunger, and severe obesity due to an impaired MC4R pathway, which may be caused by traumatic injury or genetic variants. The MC4R pathway is an endocrine 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 diseases that is approved or authorized in the United States, European Union (EU) and Great Britain. IMCIVREE is approved 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 monogenic or syndromic obesity due to: (i) proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency as determined by an FDA-approved test demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS); or (ii) Bardet-Biedl syndrome (BBS). The European Commission (EC) and Great Britain's Medicines & Healthcare Products Regulatory Agency (MHRA) have authorized IMCIVREE for the treatment of obesity and the control of hunger associated with genetically confirmed BBS or genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. In addition to the United States, we have achieved market access for

IMCIVREE for BBS or POMC and LEPR deficiencies, or both, in eight countries outside the United States, and we continue to collaborate with authorities to achieve access in additional markets.

In addition to initial commercial efforts, we are advancing what we believe is the most comprehensive clinical research program ever initiated in MC4R pathway diseases, with multiple ongoing and planned Phase 2 and Phase 3 clinical trials evaluating setmelanotide. We are developing IMCIVREE to address additional patients with acquired hypothalamic obesity and additional MC4R pathway diseases caused by genetic variants in an effort to expand the approved indications and to bring this potential therapy to approximately 53,000 estimated patients in the United States and a similarly-sized patient population in Europe. Following a Phase 2 trial in which 16 of 18 patients with hypothalamic obesity achieved the primary endpoint with a body mass index (BMI) decrease greater than 5 percent on setmelanotide therapy, and in which we observed a 14.5 mean percent reduction in BMI across all patients, we have initiated a Phase 3 trial in early 2023. The ongoing pivotal Phase 3 EMANATE trial and Phase 2 DAYBREAK trial are designed to evaluate setmelanotide in several distinct, genetically defined MC4R pathway diseases. We also are conducting a Phase 3 pediatrics trial evaluating daily setmelanotide in patients between the ages of 2 and 6 and a Phase 3 switch trial evaluating a weekly formulation of setmelanotide.

We are leveraging what we believe is the largest known DNA database focused on obesity - with approximately 60,000 sequencing samples as of December 31, 2022 - to improve the understanding, diagnosis and care of people living with severe obesity due to certain variants in genes associated with the MC4R pathway. 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 4,600 to 7,500 for U.S. patients in initial FDA-approved indications, including obesity due to biallelic POMC, PCSK1 or LEPR deficiencies, and BBS. Epidemiology estimates for patients with hypothalamic obesity is between 5,000 and 10,000 in the United States, based on our analysis of published literature and our epidemiology estimates for the indications being studied in our Phase 3 EMANATE trial suggest that approximately 53,000 U.S. patients with one of these genetically driven obesities have the potential to respond well to setmelanotide. 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. 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 field teams in the United States and Europe engaging with physicians who treat patients with severe obesity. We continue to bring together health care providers, patients and families with educational and awareness events. 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 177 employees in the United States and Europe as of January 31, 2023, a rapidly expanding network of key opinion leaders, and an increasing number of identified, diagnosed and treated patients, we are focused on changing the paradigm for the treatment of rare MC4R pathway diseases. Our focused disease awareness and patient finding efforts fuel the key elements of our strategy, including:

- **Ensure global access to IMCIVREE:** We are actively pursuing a global strategy for our clinical development, commercial and community building programs. In the United States, we are focused on identifying patients and working with physicians and payors to get eligible patients access to IMCIVREE. We have achieved access for IMCIVREE in eight international markets with plans to launch IMCIVREE in Germany for BBS in the second quarter of 2023. In addition, we anticipate launching IMCIVREE for BBS in The Netherlands in the second half of2023, and pending regulatory review, in Canada. In both Europe and North America, we are building a rare disease-focused organization that can be scaled as we seek marketing authorizations for additional rare MC4R pathway diseases.

- **Execute clinical development:** With our Phase 3 trial in hypothalamic obesity now underway, we are executing on several clinical trials designed to expand the reach of setmelanotide and potentially secure FDA approval and marketing authorization in Europe in additional indications. In addition to our pivotal trial in

hypothalamic obesity, our Phase 3 EMANATE trial, Phase 3 pediatrics trial and Phase 2 DAYBREAK trial all are ongoing. With our genetic testing programs in both the United States and Europe, 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. We will continue to expand our genetic testing effort focusing initially on clinical trial enrollment and early commercialization efforts.

- **Lifecycle development and pipeline expansion:** We are developing follow-on product candidates, including a weekly formulation of setmelanotide as well as an auto-injector, designed to be more convenient and patient-friendly. Additionally, we anticipate reporting topline data in 2023 from our clinical trial in pediatric patients from 2 years to younger than 6 years of age, potentially enabling us to reach younger patients. And we are conducting investigational new drug (IND)-enabling studies with MC4R agonist candidates that may be more selective and more potent than setmelanotide. Lastly, we will leverage our rare disease capabilities and opportunistically evaluate other investigational therapies for rare disease that offer the potential of a meaningful solution to a clear unmet medical need.

Market Overview

Severe Obesity, Hyperphagia, and the MC4R Pathway

All obesity is not the same, and rare MC4R pathway diseases are distinct from general obesity. The hallmark characteristics of rare MC4R pathway diseases are severe obesity and hyperphagia, a pathological and insatiable hunger that drives a severe preoccupation with food and extreme food-seeking behaviors. Lifestyle interventions are not therapeutic in patients with these diseases because they fail to address the underlying genetic or acquired impairment of central energy regulation and satiety.

Accordingly, the discovery that the MC4R pathway regulates both energy intake (hunger) and energy expenditure has made it an important target for therapeutics. Studies have shown that injuries to the hypothalamus region of the brain in patients with certain cancers impair MC4R signaling, leading to increased hunger, reduced energy expenditure and rapid onset of severe obesity. In addition to obesity due to POMC, PCSK1 or LEPR deficiencies and BBS, 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 certain variants of the *POMC*, *PCSK1*, *LEPR*, *SRC1* and *SH2B1* genes, as well as MC4R deficiency obesity and deficiencies in many 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 and acquired injury affecting the MC4R pathway. We believe that this approach has the potential to provide clinically-meaningful improvements in obesity and hyperphagia by re-establishing lost function in the MC4R pathway.

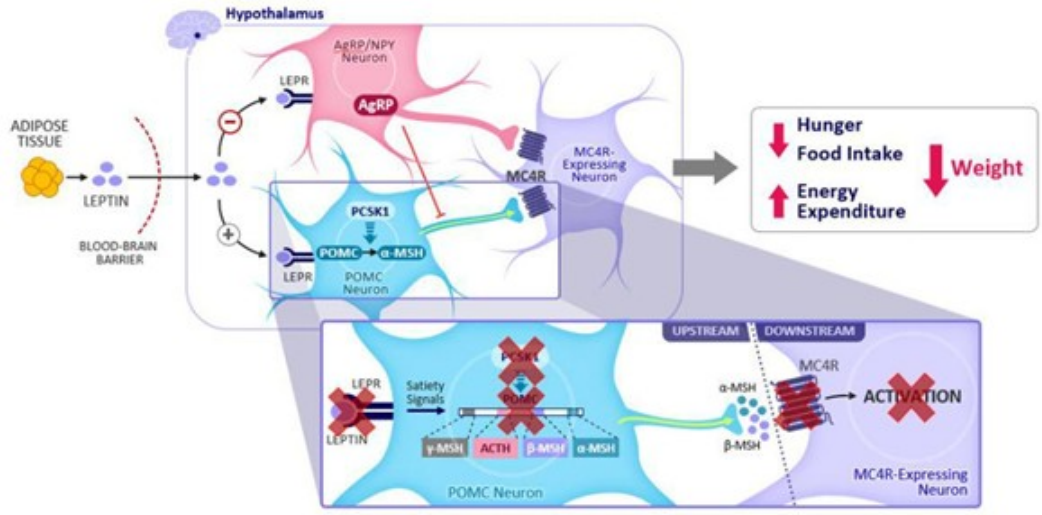
Rare MC4R Pathway Diseases

The MC4R pathway has been the focus of extensive scientific investigation for many years. This neuro-endocrine pathway in the hypothalamus is a key signaling pathway responsible for regulating hunger, food or caloric intake, and energy expenditure, which consequently affects body weight. It is known to be a critical component in the regulation of energy balance. 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, traumatic injuries or lesions disrupt this pathway, it can lead to insufficient MC4R activation and downstream signaling; the result of which is hyperphagia, reduced energy expenditure 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 as a precision treatment for rare MC4R pathway diseases. In addition to acquired hypothalamic obesity, we are evaluating setmelanotide in Phase 2 and 3 trials for the treatment of obesity due to variants in one of numerous 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 MC4R Pathway Diseases

While obesity is a global epidemic, we are focused on rare MC4R pathway diseases. Impairment of the MC4R pathway is characterized by hyperphagia and rapid-onset obesity or presence of early-onset, severe obesity. 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 onset between the ages of 2 and 5 years old. The tables below summarizes the estimated population sizes for indications currently approved or under pivotal clinical investigation.

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).

Approved by the U.S. FDA and authorized by the EC and Great Britain's MHRA[a]		
	Estimated U.S. population	Estimated European population
Bardet-Biedl syndrome	4,000 – 5,000[b]	4,000 – 5,000[b]
Obesity due to POMC or LEPR deficiency caused by biallelic variants in the *POMC*, *PCSK1 or LEPR* genes	~600 – 2,500	Similar prevalence as U.S.[c]

a. Authorized by the EC and MHRA for use in patients six years of age and older. Approved by the FDA for use in patients six years of age and older with monogenic or syndromic obesity.

b. For BBS, prevalence estimates vary between populations, from 1 in 100,000 in northern European populations with higher prevalence rates in some additional regions throughout the world. We estimate the number of patients with BBS in the United States is between 4,000 and 5,000, with a similar number in continental Europe and the United Kingdom (UK). These estimates are based on our patient identification efforts in the United States and Europe and our proprietary genetic sequencing data, as well as our belief that BBS, like most rare diseases, is underdiagnosed. We believe the BBS health care provider network in EU member states and the UK is particularly well established and more advanced than in the United States, and based on field work, we believe there are approximately 1,500 patients diagnosed and being cared for at academic centers in Europe. Applying these population-adjusted identified patient populations to the United States and other countries with comparable population genetics supports our epidemiology estimates.

c. For POMC or LEPR deficiencies, we estimate European prevalence is similar to the United States. While our sequencing data include patients from the United States and Europe, we do not have comparable sequencing data from European countries and these estimates are therefore based on applying relative population percentages to the Rhythm-derived estimates described above.

Separately, in Canada, where our new drug submission for the treatment of obesity and control of hunger in BBS or biallelic POMC, PSCK1 or LEPR deficiency is under review, we estimate there are approximately 300 – 400 individuals with BBS. This is based on data on file, a range of prevalence estimates for BBS in Canada between 1 in 125,000 to 1 in 160,000, and a population in Canada of 38,929,902 as of July 1, 2022, according to StatsCan. Also, our prevalence estimate accounts for a reported founder effect in province of Newfoundland, where estimated prevalence is approximately 1 in 17,500 (Forsythe E, Beales PL. Eur J Hum Genet. 2013;21(1):8-13.) The prevalence of POMC, PCSK1, and LEPR deficiency obesity is not well characterized as very little data are available.

Setmelanotide currently being evaluated in Phase 3 trials		
	Estimated U.S. population	Estimated European population
Acquired hypothalamic obesity	5,000 – 10,000[d]	3,500 – 10,000[e]
Obesity due to POMC insufficiency caused by heterozygous variants in the *POMC* or *PCSK1* genes	6,000[f]	Similar prevalence as U.S.[f]
Obesity due to LEPR insufficiency caused by heterozygous variants in the *LEPR* gene	4,000 [f]	Similar prevalence as U.S. [f]
Obesity due to SRC1 deficiency caused by a variant in the NCOA1 gene (SRC1 deficiency obesity)	~20,000 [f]	Similar prevalence as U.S. [f]
Obesity due to SH2B1 deficiency caused by a variant in the SH2B1 gene or 16p11.2 deletion encompassing the SH2B1 gene (SH2B1 deficiency obesity)	~23,000 [f]	Similar prevalence as U.S. [f]

d. For hypothalamic obesity in the United States, our internal Company estimates are 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.)

e. Our European prevalence estimate for hypothalamic obesity is limited to the EU4, UK and the Netherlands. The total 2020 population estimates for the six key countries (Germany, France, Spain, Italy, Netherlands, and UK) of 339,295,304 was used to reach a final prevalence of 0.1-0.3 in 10,000 patients.

f. 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 these monogenic indications. For the four rare MC4R pathway diseases we are studying on the Phase 3 EMANATE trial (POMC insufficiency, LEPR insufficiency, SRC1 deficiency and SH2B1 deficiency), we believe that the patient populations in continental Europe and UK 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 sequencing data from European countries and these estimates are therefore based on applying relative population percentages to the Rhythm-derived estimates described above. We recently updated our prevalence estimates in 2021 based on sequencing data from 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.

Limitations of Current Therapies

Although drugs approved for general obesity potentially can be used in patients with obesity and rare MC4R pathway diseases, all currently available products have limited efficacy and treat symptoms without addressing the

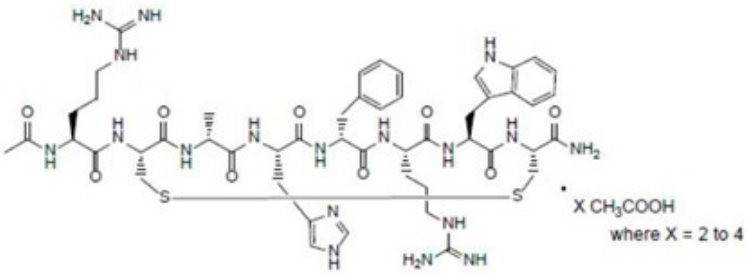
underlying biology of MC4R impairment. For example, drugs which delay gastric emptying may cause a patient to feel full and eat less, but are also often associated with nausea and vomiting as a consequence of the delayed emptying. In the case of individuals with rare MC4R pathway diseases, these therapies 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 rare MC4R pathway diseases for the same reason.

IMCIVREE™ (setmelanotide)

IMCIVREE is approved by the FDA for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndromic obesity due to: (i) POMC, PCSK1 or LEPR deficiency as determined by an FDA-approved test demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or VUS; or (ii) BBS. The EC and Great Britain's MHRA have authorized setmelanotide for the treatment of obesity and the control of hunger associated with genetically confirmed BBS or genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. IMCIVREE is the only therapeutic specifically approved for patients with these diseases. As an MC4R agonist, IMCIVREE is designed to restore impaired MC4R pathway activity arising due to genetic impairments upstream of the MC4R.

IMCIVREE contains setmelanotide acetate, a 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 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.

Bardet-Biedl syndrome

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.

Pivotal Phase 3 Clinical Trial Evaluating Setmelanotide in BBS

We announced FDA approval for IMCIVREE for BBS on June 16, 2022; EC marketing authorization for BBS on September 6, 2022; and MHRA marketing authorization for BBS on November 21, 2022. These approvals and marketing authorizations were 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. IMCIVREE was not approved for Alström syndrome, a monogenic disease that causes hyperphagia and obesity beginning in early childhood, as well as progressive vision loss, deafness, cardiomegaly, insulin resistance and other signs and symptoms.

As we announced on November 8, 2022, the pivotal data that formed the basis for IMCIVREE's approvals in BBS were published in the peer-reviewed journal *The Lancet Diabetes and Endocrinology*. As previously disclosed, treatment with setmelanotide resulted in significant weight and hunger reductions after one year of treatment among patients with BBS. The primary endpoint was achieved by 32.3% (95% confidence interval (CI), 16.7%, 51.4%; p=0.0006) of patients ≥12 years old, all of whom were patients with BBS. Data highlights among patients with BBS (n=32) after 52 weeks of setmelanotide include:

- Fifteen (15) patients ≥18 years achieved a mean (SD) percent reduction in BMI of -9.1% (6.8%; 95% CI, −13.4%, −4.8%);
- Fourteen (14) patients <18 years achieved a mean (SD) change in BMI Z score of −0.8 (0.5; 95% CI, −1.0, −0.5), and 12 patients (85.7%) achieved ≥0.2-point reduction in BMI Z; and
- Fourteen (14) patients ≥12 years who reported hunger scores achieved reduction of -30.5% in maximal hunger score.

The safety results observed in this study were consistent with that observed with setmelanotide in previous clinical trials in patients with other rare MC4R pathway diseases. Skin hyperpigmentation (n=23; 60.5%) was the most common adverse event (AE). Two patients experienced serious AEs, neither of which was considered related to setmelanotide treatment.

Also on November 21, 2022, we announced that Health Canada accepted for review our New Drug Submission (NDS) for setmelanotide, indicated in adults and pediatric patients 6 years of age and older with impairments in the MC4R pathway due to genetic diseases, for the treatment of obesity and control of hunger in BBS or biallelic POMC, PCSK1, or LEPR deficiency. Health Canada granted Priority Review of the NDS, which shortens the submission review performance target to 180 days, in comparison to 300 days for non-priority review.

Development of Setmelanotide for Additional Indications

Hypothalamic Obesity

We also are developing setmelanotide as a treatment for hypothalamic obesity, a severe obesity that arises from mechanical hypothalamic injury, for which there are no approved therapies. In 2022, setmelanotide demonstrated potential to transform the care of individuals living with the rapid onset of extreme weight gain of hypothalamic obesity with clinical data that suggested setmelanotide treatment resulted in significant, durable weight loss.

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 hypothalamic obesity display a 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.

In 2022, we achieved several milestones in our development program for hypothalamic obesity: setmelanotide received Breakthrough Therapy Designation from the FDA for hypothalamic obesity; we reported positive Phase 2 results and long-term extension trial data in hypothalamic obesity, as presented at The Obesity Society's ObesityWeek® 2022 conference in San Diego on November 2, 2022; and we reached alignment with the FDA on a Phase 3 trial design.

On March 1, 2023, we announced that our pivotal Phase 3 trial evaluating setmelanotide in patients with acquired hypothalamic obesity has been initiated, with patient screening underway. We plan to enroll 120 patients with hypothalamic obesity aged 4 years or older randomized 2:1 to setmelanotide therapy or placebo for a total of 60 weeks, including up to eight weeks for dose titration. The primary endpoint is the percent change in BMI after 52 weeks on a therapeutic regimen of setmelanotide versus placebo.

The Phase 2 study enrolled 18 patients with hypothalamic obesity caused by structural hypothalamic damage secondary to craniopharyngioma or other benign brain tumor types, surgical resection, and/or chemotherapy. Patients were between 6 and 40 years old with a body mass index (BMI) ≥95th percentile (children 6 to <18 years) or ≥35 kg/m2 (adults ≥18 years). The primary endpoint was the proportion of patients who achieved a 5 percent or greater reduction in BMI after 16 weeks of treatment. Hunger was also assessed daily, as self-reported by individual patients. Highlights from the data as presented at ObesityWeek include:

- 89 percent (16 of 18) patients evaluable for assessment had ≥5% reduction in BMI (P<0.0001; confidence interval, 69%-98%);
- 78 percent (14 of 18) patients had a 10% or greater reduction in BMI at 16 weeks;
- 14.5 mean percent reduction in BMI (N=18) at Week 16 from baseline;
- 12.6 mean percent reduction body weight (N=18) at Week 16 from baseline;
- Mean (standard deviation [SD]) BMI Z score at Week 16 was 2.7 (1.3) (n=13 pediatric patients), a reduction of 1.3 (1.0) points from baseline; and
- Mean (SD) most hunger score at baseline was 6.6 (1.6), compared with 3.7 (2.5) at Week 16, for a reduction of –2.9 (2.3) points or 45% for patients ≥12 years of age (n=11).

Consistent with prior clinical experience in other rare MC4R pathway diseases, setmelanotide was observed to be generally well tolerated. The most common adverse events (AEs) included nausea (61.1%), vomiting (33.3%), skin hyperpigmentation (33.3%), diarrhea (22.2%), and COVID-19 (22.2%). Two patients discontinued due to AEs and a third patient was non-compliant.

At ObesityWeek, we also reported data from patients with hypothalamic obesity who enrolled in our long-term extension trial. The presentation included data on patients who continued on setmelanotide therapy in our open-label, long-term extension trial after completing 16 weeks on setmelanotide therapy in the Phase 2 trial. A total of 14 patients continued on therapy in this long-term extension trial. As of a cut-off date of September 23, 2022, of these patients:

- 13 patients who reached a total of 29 weeks on setmelanotide therapy achieved a mean BMI reduction of 21.1% (SD, 11.2%); and

- Five (5) patients who reached a total of 41 weeks on setmelanotide therapy achieved a mean BMI reduction of 26.7% (SD, 12.4%).

Additional MC4R Pathway Genetic Variants

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 60,000 sequencing samples as of December 2022 - to improve the understanding, diagnosis and care of people living with hyperphagia and 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 MC4R pathway diseases, 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 exploratory Phase 2 Basket Study evaluating setmelanotide in patients with severe obesity driven by variants in several different MC4R pathway associated genes, in 2022 we initiated the pivotal Phase 3 EMANATE clinical trial to evaluate setmelanotide in four 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 10 genes with strong or very strong relevance to the MC4R pathway.

Phase 3 EMANATE Trial

The ongoing pivotal Phase 3 EMANATE clinical trial is a randomized, double-blind, placebo-controlled trial, designed to evaluate setmelanotide in four 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. The epidemiology estimates for the indications being studied in our Phase 3 EMANATE trial suggest that approximately 53,000 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 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 SH2B1 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 removes 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 Phase 2 Basket Study was an open label study designed to evaluate setmelanotide in patients with obesity defined as BMI $\geq$ 30 kg/m^2 for patients 16 years of age or older or BMI$\geq$ 95th percentile for age and gender for patients between 6 and 16 years old. Patients were stratified by cohort according to their genetic variant. The primary endpoint of the study was 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 VUS. As genetics of obesity remains an emerging field, the vast majority of variants in genes associated with the MC4R pathway are classified as VUS. 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.

- 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 our now concluded Phase 2 Basket Study, we also evaluated setmelanotide in 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).

On October 12, 2022, at the inaugural International Meeting on Pathway-Related Obesity: Vision of Excellence (IMPROVE) 2022 in Berlin, Germany, we reported data from a cohort of patients with MC4R deficiency obesity in the Phase 2 Basket Study. We believe these data represent an important step toward understanding the impact that gene variants can have on MC4R pathway function and its regulation of hunger, energy expenditure and body weight. The results suggest that patients with certain variants of the MC4R gene could benefit from treatment with setmelanotide, while highlighting limitations in the predictive value of an in vitro assay designed to identify which variants should be considered rescuable or nonrescuable. Overall, 23 patients with predicted rescuable MC4R deficiency and 24 patients with predicted nonrescuable MC4R deficiency were enrolled in two cohorts within our exploratory Basket Study and all reached three months of treatment with setmelanotide. The in vitro assay demonstrated limited predictive value for setmelanotide response, which was defined as ≥5% body mass index (BMI) reduction after three months treatment. Data highlights include:

- 7 of 23 patients (30.4%) with MC4R variants predicted to be rescuable achieved a ≥5% BMI reduction at Month 3 (90% confidence interval (CI), 15.3%-49.6%);
- Most responders (6 of 16) were carriers of the p.S127L heterozygous variant in the rescuable group;
- 3 of 24 patients (12.5%) with MC4R variants predicted to be nonrescuable achieved ≥5% BMI reduction at Month 3 (90% CI, 3.5%-29.2%); and
- Weight loss, as determined by percent change in BMI, tended to increase over time in patients achieving ≥5% BMI reduction at Month 3, with continued weight loss in responders in both predicted rescuable and nonrescuable groups at Month 6 and Month 9 of treatment with setmelanotide,

The safety results observed in this study were consistent with those observed with setmelanotide in previous clinical trials in patients with other rare MC4R pathway diseases. We plan to continue our assessment of the genetics of the MC4R pathway and opportunities to identify patients who we believe may benefit from setmelanotide.

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 December 2021, we initiated a Phase 3 trial to evaluate the weekly formulation of setmelanotide in patients with rare MC4R pathway diseases. 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 up to 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 study is intended to provide detailed pharmacokinetic characterization of the weekly formulation. 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. We anticipate announcing topline data from this ongoing Phase 3 trial in the second half of 2023.

In addition, in 2023, we plan to initiate a second trial to evaluate the weekly formulation of setmelanotide. 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 a maximum tolerated dose 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 18 weeks of once weekly dosing.

These trials follow an earlier trial that evaluated the weekly formulation of setmelanotide. Data from this trial, presented in October 2021, 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.

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 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.

Over the course of our clinical development program, a total of 764 patients who participated in our trials have received the daily or weekly formulation of setmelanotide, including 13 patients who had been on setmelanotide therapy for more than five years, as of November 24, 2022:

Duration of Setmelanotide Therapy	Number of patients
<1 year	569
≥1 year	195
>2 years	118
>3 years	63
>4 years	30
>5 years	13
Total	764

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 certain patients 6 years of age and older. Rare MC4R pathway diseases 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. On August 2, 2022, we announced that we completed enrollment in our 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

European Medicines Agency (EMA) to modify our EMA-approved Pediatric Investigation Plan (PIP) to be consistent with our plans for the treatment of these younger patients.

We have an ongoing program to identify next generation MC4R agonist candidates that may be more selective and more potent than setmelanotide. 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.

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 60,000 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 (URO) or Rare Obesity Advanced Diagnosis (ROAD). More than 90% of our DNA sequencing database is derived from the U.S. population. Therefore, our estimates of patient populations in Canada and Europe are more preliminary, but we believe prevalences of these genetic diseases are similar to those in United States. 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, or URO, our free genetic testing program designed to help determine if individuals have an underlying genetic cause of their severe obesity, is 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..

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 U.S. partner, Prevention Genetics, a subsidiary of Exact Sciences Corp., 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.

In 2022, we launched a new free genetic testing program similar to the URO program covering certain European markets called ROAD. The ROAD program is mirroring the URO program to increase awareness on rare genetic diseases of obesity and support patient identification in the International region. As of December 31, 2022, we have collected and sequenced approximately 2,000 samples from individuals with severe obesity from seven countries, including Spain, Italy, Ireland, Israel, Turkey and Germany. Our partner CGC Genetics Unilabs conducts the genetic testing for ROAD. This program covers the cost of the test, the kit and shipment.

As of December 31, 2022, we had collected and analyzed more than 25,000 genetic samples from individuals with severe obesity with URO or ROAD, including approximately 13,000 during the year ended December 31, 2022.

Commercial Efforts for IMCIVREE

We are focused on making IMCIVREE available globally.

In the United States, IMCIVREE was initially approved by the FDA in November 2020 for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to POMC, PCSK1 or LEPR deficiency as determined by an FDA-approved test demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or VUS, and the FDA expanded the label to include BBS in June 2022. The initial approval allowed us to develop commercial infrastructure, build relationships with physicians and payers and deliver commercial product to patients. With the label expansion to include BBS, we executed – and continue to execute – on our rare disease launch strategy of engaging with the community, speeding diagnosis of BBS and educating on the benefits of IMCIVREE therapy. Our team remains focused on identifying patients with BBS, the physicians who care them and driving prescriptions for IMCIVREE. Additionally, through Rhythm InTune, our U.S. support services program which we launched in June 2022, we provide personalized support for patients and families living with rare MC4R pathway diseases. With education and resources tailored to fit unique needs, each patient and family is matched with a dedicated patient education manager as a single point of contact to provide treatment support by educating patients and their health care providers, navigating insurance coverage as they start treatment, providing injection support and offering education on what to expect.

Additionally, our North America team anticipates completion of a regulatory review via Health Canada's priority review process and, pending approval, making IMCIVREE commercially available in Canada for adult and pediatric patients 6 years of age and older with impairments in the MC4 receptor pathway due to genetic diseases, for the treatment of obesity and control of hunger in BBS, POMC, PSCKI and LEPR in 2023.

Internationally, we have achieved access for IMCIVREE in eight markets: for patients with BBS or POMC, PCSK1 or LEPR deficiency in France through paid early access; for patients with POMC, PCSK1 or LEPR deficiency in Germany, the UK, the Netherlands and Italy; and for patients with POMC, PCSK1 or LEPR deficiency through named patient sales in Austria and Turkey and for patients with MC4R pathway diseases and BBS through early access in Argentina. We anticipate launching IMCIVREE in Germany for BBS in the first half of 2023, as well as in The Netherlands in 2023, and in Spain (Spanish launch to include POMC and LEPR deficiencies as well as BBS) in 2024.

While we are focused on commercial access for IMCIVREE for BBS and POMC and LEPR deficiencies, we are working with the broader community of patients and families, physicians, scientists and more to engage with them on the impact of hyperphagia and severe obesity caused by rare MC4R pathway diseases. Individually, populations with each of these MC4R pathway diseases are rare, and affected patients face many of the same challenges as any classically rare disease patient populations. There is little or no awareness about rare MC4R pathway diseases, 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.

Xinvento B.V. Acquisition

On February 27, 2023, we completed the acquisition of Xinvento B.V., or Xinvento, a Dutch private limited liability company based in the Netherlands, through our wholly-owned subsidiary Rhythm Pharmaceuticals Netherlands B.V., a Dutch private limited liability company. Xinvento was founded in 2021 by Claudine van der Sande and is developing novel investigational therapeutic candidates designed to improve the care congenital hyperinsulinism (CHI).

CHI is the most frequent cause of severe, random and persistent hypoglycemia in newborns and children. Hypoglycemia results from an over-secretion of insulin, which causes blood sugar levels to fall dangerously low. Without proper and immediate treatment, children with CHI may suffer seizures, coma, or even death and, longer term, patients may experience developmental delays, epilepsy, cerebral palsy, and other neurological damage. In the United States, the estimated incidence rate for CHI is 1:29,000 to 1:31,000, according to the literature. We aim to develop treatment options for these individuals and expect to initiate clinical development of a new therapeutic candidate in 2024.

For more information about the acquisition of Xinvento, see Part II, Item 9B. “Other Information.”.

Competition

The biotechnology and pharmaceutical industries are intensely competitive and subject to rapid and significant technological change. We have competitors with general obesity medications 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 BBS or POMC, PCSK1 or LEPR deficiencies, and there are no other approved treatments for addressing hyperphagia related behaviors of patients with rare MC4R pathway diseases. Bariatric surgery is not an appropriate treatment option for these MC4R pathway diseases 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 and those in clinical development for the same, 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, do not specifically restore function impaired by genetic deficiencies and trauma to the hypothalamus that disrupt MC4R pathway signaling, which we believe is a root cause of hyperphagia and obesity in patients with these diseases.

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, 2022, we have paid $4.0 million in clinical and regulatory milestones and $9.0 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, 2022, we have made $2.3 million of milestone payments to Camurus. 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. We have notified Takeda that we have halted development activities related to RM-853.

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 four independent sub-studies in patients with obesity due to a heterozygous variant of POMC/PCSK1 or LEPR; certain variants of the SRC1 gene, and certain variants of the SH2B1 gene. According to the terms of the RareStone License, RareStone made an upfront payment to Rhythm of $7.0 million and issued Rhythm 1,077,586 ordinary shares. 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.

On October 28, 2022, we delivered written notice, or the Notice, to RareStone that we have terminated the RareStone License for cause. In accordance with the Notice, we maintain that RareStone has materially breached its obligations under the RareStone License to fund, perform or seek certain key clinical studies and waivers, including with respect to our global EMANATE trial, among other obligations. On December 21, 2022, RareStone provided written notice to us that it objects to the claims in the Notice, including our termination of the RareStone License for cause.

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 ten 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 16 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, 2022, the portfolio for the MC4 program consists of 14 issued United States patents and 271 issued non-United States patents across 8 of the 13 families. There also 15 pending United States patent applications and 82 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 4 issued United States patents and 134 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 and yielded 1 issued United States patent and 2 non-United States patents. 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 Canada, China, Europe, and Japan. 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 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. 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.

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.

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.

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 confirmatory 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 confirmatory studies in a timely manner 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. Clinical trials for which an application was submitted (i) prior to January 31, 2022 under the Clinical Trials Directive, or (ii) between January 31, 2022 and January 31, 2023 and for which the sponsor has opted for the application of the Clinical Trials Directive remain governed by said Directive until January 31, 2025. After this date, all clinical trials (including those which are ongoing) will become subject to the provisions of the CTR.

Medicines used in clinical trials must be manufactured in accordance with Good Manufacturing Practice (GMP). Other national and EU-wide regulatory requirements may also apply..

Marketing Authorizations

In the EU, medicinal product candidates can only be commercialized after obtaining a marketing authorization, (MA). To obtain regulatory approval of a product candidate in the EU, we must submit a marketing authorization application, (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 (EC) 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 "standard" 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 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 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 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 EC 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, under the Retained EU Law (Revocation and Reform) Bill 2022, which is currently before the UK parliament, any retained EU law not expressly preserved and "assimilated" into domestic law or extended by ministerial regulations (to no later than 23 June 2026) will automatically expire and be revoked by December 31, 2023. In addition, new EU 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 favor 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.

There will be no pre-MA orphan designation. Instead, the MHRA will review applications for orphan designation in parallel to the corresponding MA application. The criteria are essentially the same, but have been tailored for the market, i.e., the prevalence of the condition in Great Britain, rather than the EU, must not be more than five in 10,000. Should an orphan designation be granted, the period or market exclusivity will be set from the date of first approval of the product in Great Britain.

Additionally, on June 26, 2022, the MHRA published its response to a 10-week 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. Regulations implementing the new regime were originally scheduled to come into force in July 2023, but have recently been postponed to July 2024. Devices bearing CE marks issued by EU notified bodies under the MDR or MDD are now subject to transitional arrangements. In its consultation response, the MHRA indicated that the future UK regulations will allow devices certified under the MDR to be placed on the market in Great Britain under the CE mark until either the certificate expires or for five years after the new regulations take effect, whichever is sooner. Devices certified under the MDD could continue to be placed on the market until either the certificate expires or for three years after the new regulations take effect, whichever is sooner. Following these transitional periods, it is expected that all medical devices will require a UK Conformity Assessed (UKCA) mark. Manufacturers may choose to use the UKCA mark on a voluntary basis until June 30, 2023. However, UKCA marking will not be recognized in the EU. The rules for placing medical devices on the market in Northern Ireland, which is part of the UK, differ from those in the rest of the UK. Compliance with this legislation is a prerequisite to be able to affix the UKCA mark to our products, without which they cannot be sold or marketed in GB.

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. We are also enrolled in the Medicaid Drug Rebate Program and other governmental pricing programs, and have price reporting and payment obligations under these programs.

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.

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 Laws

Numerous state, federal and foreign laws, regulations and standards govern the collection, use, access to, confidentiality and security of health-related and other personal information, and could apply now or in the future to our operations or the operations of our partners. In the United States, numerous federal and state laws and regulations, including data breach notification laws, health information privacy and security laws and consumer protection laws and regulations govern the collection, use, disclosure, and protection of health-related and other personal information. In addition, certain foreign laws govern the privacy and security of personal data, including health-related data. Privacy and security laws, regulations, and other obligations are constantly evolving, may conflict with each other to complicate compliance efforts, and can result in investigations, proceedings, or actions that lead to significant civil and/or criminal penalties and restrictions on data processing.

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;

- 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;

- established the Medicare Part D coverage gap discount program, which require 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

- 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.

In addition, 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, which went into effect on April 1, 2013 and will remain in effect through 2032, 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. On March 11, 2021, the American Rescue Plan Act of 2021 was signed into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug's AMP, beginning January 1, 2024.

Most significantly, on August 16, 2022, President Biden signed the Inflation Reduction Act of 2022 (IRA) into law. This statute marks the most significant action by Congress with respect to the pharmaceutical industry since adoption of the ACA in 2010. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of the Department of Health and Human Services (HHS) to implement many of these provisions through guidance, as opposed to regulation, for the initial years. For that and other reasons, it is currently unclear how the IRA will be effectuated, and while the impact of the IRA on the pharmaceutical industry cannot yet be fully determined, it is likely to be significant.

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.

In the EU, On December 15, 2021, Regulation No 2021/2282 on HTA, amending Directive 2011/24/EU, was adopted. This regulation which entered into force in January 2022 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.

Human Capital

Our employees are dedicated to our mission to transform the lives of patients and their families living with hyperphagia and severe obesity caused by rare MC4R pathway diseases by rapidly advancing care and precision medicines addressing the root cause. As of January 31, 2023, we had 177 employees, including 143 in the United States and 34 in nine countries outside the United States. 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. Since the COVID-19 pandemic, we have maintained 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, and you should not consider information on our website to be part of this Annual Report.

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 primarily focused on developing and commercializing IMCIVREE® (setmelanotide) to treat patients living with hyperphagia and severe obesity caused by rare MC4R pathway diseases. Our business activities have included 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 generated less than $25.0 million of revenue from product sales. In the United States, IMCIVREE is approved for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndromic obesity due to pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency as determined by a U.S. Food and Drug Administration (FDA)-approved test demonstrating variants in POMC, PCSK1 or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance, or Bardet-Biedl syndrome (BBS). The European Commission (EC) has authorized setmelanotide for the treatment of obesity and the control of hunger associated with genetically confirmed BBS or genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. The UK's Medicines & Healthcare Products Regulatory Agency (MHRA) authorized setmelanotide for the treatment of obesity and the control of hunger associated with genetically confirmed BBS or 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 are continuing to transition 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 transition. We are still at the early stages of demonstrating 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 EC and the MHRA, as noted above, and is in development to address patients affected by 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 $181.1 million and $69.6 million for the years ended December 31, 2022 and 2021, respectively. As of December 31, 2022, we had an accumulated deficit of $710.1 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 expect to continue to incur significant sales, marketing and outsourced manufacturing expenses. We have and will continue to incur additional costs associated with operating as a public company. 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 generated less than $25.0 million of revenue from product sales. Our ability to generate revenue depends on a number of factors, including, but not limited to, our ability to:

- continue to commercialize setmelanotide by building a commercial organization and/or entering into collaborations with third parties;
- ensure setmelanotide is available to patients;
- continue to 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 deficiencies affecting the MC4R pathway; and
- successfully manufacture or contract with others to manufacture setmelanotide.

Absent our entering into collaboration or partnership agreements, we have and expect to continue to incur significant sales and marketing costs as we continue to commercialize setmelanotide. Even though IMCIVREE is FDA approved and authorized by the EMA and MHRA for certain indications, 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. As of result of the acquisition of Xinvento B.V., we expect to devote substantial financial resources to the research and development and potential commercialization of a therapeutic product candidate for CHI. We may not achieve profitability soon after generating product sales, if ever. If we are unable to generate significant 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 BBS, 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, as well as in connection with research and development activities as a result of the acquisition of Xinvento B.V. in February 2023. We intend to use our available cash resources to advance the clinical development of setmelanotide, for disease-education and community-building activities, 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 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 October 2022, we raised aggregate net proceeds of approximately $742.6 million through the issuance of our common stock after deducting underwriting discounts, commissions and offering related transaction costs. We 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. In June 2022, we entered into a Revenue Interest Financing Agreement, or RIFA, with HealthCare Royalty Partners for a total investment amount of up to $100 million, conditioned upon our achievement of certain clinical development and sales milestones. As of December 31, 2022, we have received $72.3 million of aggregate proceeds, net of debt issuance costs, under the RIFA. As of December 31, 2022, our cash and cash equivalents and short-term investments were approximately $333.3 million. We expect that our existing cash and cash equivalents and short-term investments will be sufficient to fund our operations into 2025. 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 supply chain issues and labor shortages, rising inflation and interest rates and international turmoil due to the Russian invasion of Ukraine, 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.

Our Revenue Interest Financing Agreement with Healthcare Royalty Partners could restrict our ability to commercialize IMCIVREE, limit cash flow available for our operations and expose us to risks that could adversely affect our business, financial condition and results of operations.

On June 16, 2022, we entered into the RIFA, with entities managed by HealthCare Royalty Management, collectively referred to as the Investors. Pursuant to the RIFA and subject to customary closing conditions, the Investors agreed to pay the Company an aggregate investment amount of up to $100.0 million, or the Investment Amount. Under the terms of the RIFA, we received $37.5 million on June 29, 2022 upon FDA approval of IMCIVREE in BBS, and an additional $37.5 million on September 29, 2022, following EC marketing authorization for BBS on September 6, 2022. We are entitled to receive the remaining $25.0 million of the Investment Amount forty-five business days following achievement of a specified amount of cumulative net sales of IMCIVREE between July 1, 2022 and September 30, 2023.

As consideration for the Investment Amount and pursuant to the RIFA, we agreed to pay the Investors a tiered royalty on our annual net revenues, or Revenue Interest, including worldwide net product sales and upfront payments and milestones. The applicable tiered percentage will initially be 11.5% on annual net revenues up to $125 million, 7.5% on annual net revenues of between $125 million and $300 million and 2.5% on annual net revenues exceeding $300 million. If the Investors have not received cumulative minimum payments equal to 60% of the amount funded by the Investors to date by March 31, 2027 or 120% of the amount funded by the Investors to date by March 31, 2029, we must make a cash payment immediately following each applicable date to the Investors sufficient to gross the Investors up to such minimum amounts after giving full consideration of the cumulative amounts paid by us to the Investors through each date.

The Investors' rights to receive the Revenue Interests will terminate on the date on which the Investors have received payments equal to a certain percentage of the funded portion of the Investment Amount including the aggregate of all payments made to the Investors as of such date, each percentage tier referred to as the Hard Cap, unless the RIFA is earlier terminated. The total Revenue Interests payable by us to the Investors is capped between 185% and 250% of the Investment Amount paid to us, dependent on the aggregate royalty paid between 2028 and 2032. If a change of control of occurs, the Investors may accelerate payments due under the RIFA up to the Hard Cap plus any other obligations payable under the RIFA.

Our obligations under the RIFA could have significant negative consequences for our security holders and our business, results of operations and financial condition by, among other things:

- increasing our vulnerability to adverse economic and industry conditions;
- limiting our ability to obtain additional financing or enter into IMCIVREE partnership agreements;
- requiring the dedication of a portion of our cash flow from operations to service our indebtedness, which will reduce the amount of cash available for other purposes;
- limiting our flexibility to plan for, or react to, changes in our business;
- placing us at a possible competitive disadvantage with competitors that are less leveraged than us or have better access to capital; and
- if we fail to comply with the terms of the RIFA, resulting in an event of default that is not cured or waived, Investors could seek to enforce their security interest in our cash and cash equivalents and all assets relating to IMCIVREE that secures such indebtedness.

To the extent we incur additional debt (including without limitation additional amounts under the RIFA), the risks described above could increase.

Risks Related to the Development of Setmelanotide

Positive results from earlier 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: BBS; 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 April 2022 we enrolled the first patient our pivotal Phase 3 EMANATE clinical trial of setmelanotide. The trial is a randomized, double-blind, placebo-controlled study with four independent sub-studies evaluating setmelanotide in patients with: heterozygous POMC/PCSK1 obesity; heterozygous LEPR obesity; certain variants of the SRC1; or certain variants of SH2B1 genes. After receiving feedback from the FDA in April 2022 that indicated that additional clinical trials to support potential registration for non-rare patient populations would likely be required, we eliminated a fifth sub-study intended to evaluate setmelanotide in patients with a PCSK1 N221D variant. Each of the four sub-studies 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 EC 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. 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 individuals with severe obesity that provide another approach to estimating prevalence. As of December 31, 2022, our database had approximately 60,000 sequencing samples. 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. 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, 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. 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, of approximately 0.09%.

- *Bardet-Biedl Syndrome*. Our addressable patient population estimate for BBS is approximately 4,000 to 5,000 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;

  - comparisons to our patient identification efforts in Europe where we believe there are approximately 1,500 patients diagnosed and being cared for at academic centers in Europe;

  - our patient identification efforts to date in the United States;

  - our internal sequencing yield for biallelic pathogenic or likely pathogenic variants in BBS genes of approximately 0.3%; 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.

- *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 suspected pathogenic is approximately 53,000 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 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.

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 5,000 to 10,000 patients in the United States. This estimate is based on:

  - diagnosis of an underlying HO etiology such as craniopharyngioma (CP), astrocytoma, or other brain tumors with CP accounting for approximately 50% of HO etiologies;

  - an annual incidence of CP of approximately 1.3 to 2.2 per million per year in the United States, which projects to approximately 600 cases of CP per year based on a United States population of approximately 329 million;

  - approximately 50% (based on a published range of 6% to 91%) of CP patients develop HO;

  - published estimates of overall survival (OS) after CP diagnosis, with a 20-year OS of 84%;

  - allowing for patients that develop HO due to other factors besides CP, results in an estimated HO prevalence after CP diagnosis in the United States exceeding 2,500-7,500 patients; and

  - internal Company estimate is based on reported incidence of hypothalamic obesity following CP and long-term survival rates.

We believe that the patient populations in the EU are similar to 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 or other public health emergencies;
- 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 or for other reasons, 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 for additional indications.

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 or opinion 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 and other public health emergencies 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 IRB at the sites where the IRBs 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.

In addition, the FDA's and other regulatory authorities' policies with respect to clinical trials may change and additional government regulations may be enacted. For instance, the regulatory landscape related to clinical trials in the EU recently evolved. 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. While the EU 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, the EU CTR introduces a centralized process and only requires the submission of a single application to all member states concerned. The EU 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 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 EU CTR foresees a three-year transition period. The extent to which ongoing and new clinical trials will be governed by the EU CTR varies. For clinical trials whose CTA was made under the EU Clinical Trials Directive before January 31, 2022, the EU Clinical Trials Directive will continue to apply on a transitional basis until January 31, 2025. Clinical trials for which an application was submitted (i) prior to January 31, 2022 under the EU Clinical Trials Directive, or (ii) between January 31, 2022 and January 31, 2023 and for which the sponsor has opted for the application of the EU Clinical Trials Directive remain governed by said Directive until January 31, 2025. After this date, all clinical trials (including those which are ongoing) will become subject to the provisions of the EU CTR. Compliance with the EU CTR requirements by us and our third-party service providers, such as CROs, may impact our developments plans.

If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies governing clinical trials, our development plans may be impacted.

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 impacted multiple countries and regions, including the United States, Canada, Europe, and China, where we have planned or ongoing preclinical studies and clinical trials. If the COVID-19 pandemic and disruptions caused by government actions to limit its spread continue 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;

- 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 contracted research and development laboratory facilities;

- 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;

- 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.

As the COVID-19 pandemic continues to evolve, the extent to which the pandemic may further impact 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. 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. Also, 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. 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 disease or condition 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 disease or condition 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 EC 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 EC 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 competent authorities 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.

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 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 EC 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 defects upstream of the MC4R in the leptin melanocortin pathway, which includes POMC deficiency obesity, LEPR deficiency obesity, Bardet-Biedl syndrome and Alström syndrome, as well as hypothalamic obesity 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 EC 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, and have initiated clinical studies 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 setmelanotide, 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, until May 25, 2022, in vitro diagnostic medical devices were regulated by Directive 98/79/EC, or the IVDD, which has been repealed and replaced by Regulation (EU) No 2017/746, or the IVDR. Unlike the IVDD, the IVDR is directly applicable in EU member states without the need for member states to implement into national law. The regulation of companion diagnostics is now subject to further requirements set forth in the IVDR. However on October 14, 2021, the EC 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 became applicable on May 26, 2022 but there is 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. For instance, class C devices (including devices that are intended to be used as companion diagnostics) have until May 26, 2026 to comply with the new requirements. 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 an EU 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 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. In June 2022, the FDA approved our supplemental NDA for the use of IMCIVREE to treat chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to BBS. 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 recently 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 December 13, 2021, Regulation No 2021/2282 on HTA, amending Directive 2011/24/EU, was adopted. While the Regulation entered into force in January 2022, it will only begin to apply from January 2025 onwards, with preparatory and implementation-related steps to take place in the interim. Once the Regulation becomes applicable, it will have a phased implementation depending on the concerned products. 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 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, EMA and UK marketing authorization for certain indications, 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 EC 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 EC;
- 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, payors 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 BBS or POMC, PCSK1 or LEPR deficiencies, and there are no approved treatments for chronic weight management in patients with deficiencies with 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 and ongoing global supply chain issues, 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.

In light of our recent election to terminate the exclusive license agreement with RareStone Group Ltd., or RareStone, the development of setmelanotide in certain indications and commercialization of IMCIVREE in certain markets could be delayed or terminated and our business could 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.

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.

On October 28, 2022, we delivered a written notice to RareStone that we have terminated the RareStone License for cause. In accordance with the notice, we maintain that RareStone has materially breached its obligations under the RareStone License to fund, perform or seek certain key clinical studies and waivers, including with respect to the Company’s global EMANATE trial, among other obligations. On December 21, 2022, RareStone provided written notice to the Company that it objects to the claims in our October 28, 2022 notice, including the Company’s termination of the RareStone License for cause. RareStone may attempt to cure the alleged breaches, which we believe to be incurable, within the timeframe specified under the RareStone License. There can be no assurance that we will be able to negotiate an appropriate cure to the alleged material breaches and, if required, we expect to seek appropriate relief under the terms of the RareStone License. Termination of, or any possible litigation focused on, the 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. To date, no such funding has been provided. If the agreement were terminated, however, we may need to refund any such potential payments and seek additional funding to support the research and development of

setmelanotide or discontinue any research and development activities for setmelanotide in China, including mainland China, Hong Kong and Macao, which could have a material adverse effect on our business.

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 of setmelanotide and commercialization of IMCIVREE;
- 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 once-weekly 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, the EU, and other countries, 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, the EU, and other countries, 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 EC, 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, PCSK1 or LEPR deficiencies, or BBS in the United States, for the treatment of obesity and the control of hunger associated with genetically confirmed BBS and confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above including patients with POMC or LEPR deficiency who have mild, moderate or severe renal impairment, and the MHRA marketing authorization for the treatment of obesity and the control of hunger associated with genetically confirmed BBS and confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. 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. In the United States, IMCIVREE is approved for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndromic obesity due to POMC, PCSK1 or LEPR deficiency as determined by a FDA-approved test demonstrating variants in *POMC*, *PCSK1* or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance, or BBS. The EC has authorized setmelanotide for the treatment of obesity and the control of hunger associated with genetically confirmed BBS or genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. The UK's MHRA authorized setmelanotide for the treatment of obesity and the control of hunger associated with genetically confirmed BBS or genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. Setmelanotide 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 EC 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 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 EC 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 EC 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 EC during the first half of 2023. The proposed revisions, once they are agreed and adopted by the European Parliament and European Council (not expected before the end of 2024 or early 2025), 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, the FDA postponed most inspections of domestic and foreign manufacturing facilities at various points. Even though the FDA has since resumed standard inspection operations of domestic facilities where feasible, 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, and any resurgence of the virus or emergence of new variants may lead to further inspectional delays. 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 UK's withdrawal from the EU, commonly referred to as Brexit, has resulted in the relocation of the EMA from the UK 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 UK. Although we have obtained FDA approval and marketing authorization from the EC 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 UK 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 UK 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. Thus, the ACA will remain in effect in its current form.

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 under the sequestration required by the Budget Control Act of 2011, which will remain in effect through 2032, unless additional Congressional action is taken. Additionally, 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. On March 11, 2021, the American Rescue Plan Act of 2021 was signed into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug's average manufacturer price, or AMP, beginning January 1, 2024.

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.

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.

Most significantly, on August 16, 2022, President Biden signed the Inflation Reduction Act of 2022 (IRA) into law. This statute marks the most significant action by Congress with respect to the pharmaceutical industry since adoption of the ACA in 2010. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of the Department of Health and Human Services (HHS) to implement many of these provisions through guidance, as opposed to regulation, for the initial years. For that and other reasons, it is currently unclear how the IRA will be

effectuated, and while the impact of the IRA on the pharmaceutical industry cannot yet be fully determined, it is likely to be significant.

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. 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.

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 every quarter for each unit of our covered outpatient drugs dispensed to Medicaid beneficiaries and paid for by a state Medicaid program. The rebate is 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 (AMP) 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. The Medicaid rebate consists of two components, the basic rebate and the additional rebate, which is triggered if the AMP for a drug increases faster than inflation. 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 AMP 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.

The recently-enacted IRA imposes rebates under Medicare Part B and Medicare Part D that are triggered by price increases that outpace inflation (first due in 2023), 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. The Medicare Part D rebate will be calculated on the basis of the AMP figures we report pursuant to the MDRP.

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 AMP and rebate 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 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 monogenic or syndromic obesity due POMC, PCSK1, or LEPR, deficiency confirmed by FDA-approved test demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance, and due to BBS. 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 has increased the likelihood, and risks associated with data breach litigation. Further, the California Privacy Rights Act, or CPRA, generally went into effect on January 1, 2023, and significantly amends the CCPA. It imposes 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 also creates a new California data protection agency authorized to issue substantive regulations and could result in increased privacy and information security enforcement. Additional compliance investment and potential business process changes may also be required. Similar laws have passed in Virginia, Utah, Connecticut 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, or in the context of our activities in the 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 EEA, 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.

Among other requirements, the GDPR and UK GDPR also regulate transfers of personal data subject to the GDPR or UK 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. In March 2022, the US and EU announced a new regulatory regime intended to replace the invalidated regulations; however, this new EU-US Data Privacy Framework has not been implemented beyond an executive order signed by President Biden on October 7, 2022 on Enhancing Safeguards for United States Signals Intelligence Activities. 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.

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 or UK 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, the UK GDPR, and other countries' privacy or data security-related laws 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 continue 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 continue to commercialize setmelanotide in foreign markets for which we intend to rely on collaborations with third parties. As we continue to 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 continue to 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 departure 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 UK, the UK formally withdrew from the EU on January 31, 2020.

Since the end of the Brexit transition period on January 1, 2021, the UK has operated under a separate regulatory regime to the EU. EU laws regarding medicinal products only apply in respect of the UK to Northern Ireland (as set out in the Protocol on Ireland/Northern Ireland). However, under the Retained EU Law (Revocation and Reform) Bill 2022, which is currently before the UK parliament, any retained EU law not expressly preserved and "assimilated" into domestic law or extended by ministerial regulations (to no later than June 23, 2026) will automatically expire and be revoked by December 31, 2023. The EU laws that have been transposed into United Kingdom law through secondary legislation remain applicable. While the UK has indicated a general intention that new laws regarding the development, manufacture and commercialization of medicinal products in the UK will align closely with EU law, there remain 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 UK and EU pharmaceutical regulations. For example, despite the UK carrying out a public consultation on future changes to the clinical trials legislation, which ended on March 14, 2022, it is still not clear the extent to which the UK will adopt legislation aligned with, or similar to, the EU CTR which became applicable in the EU 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 UK 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 authorization 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 UK marketing authorizations effective in Great Britain and issued with a UK 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 UK, the MHRA is sufficiently prepared to handle the increased volume of marketing authorization 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 UK'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 the Acquisition of Xinvento B.V.

We may fail to realize the anticipated benefits of our acquisition of Xinvento B.V., those benefits may take longer to realize than expected, and we may encounter significant integration difficulties.

In February 2023, in order to expand our pipeline and build on our focus on rare endocrinology diseases, we acquired Xinvento B.V., a Netherlands-based biotech company focused on developing therapies for congenital hyperinsulinism (CHI). We expect that the integration process will be complex, costly and time-consuming. As a result, we are devoting, and will continue to be required to devote, significant management attention and resources to integrating Xinvento B.V. into our business. The integration process may be disruptive to our business and the expected benefits may not be achieved within the anticipated time frame, or at all. The Xinvento B.V. intellectual property may not have the scientific value and commercial potential which we envision. We may not be able to integrate the two businesses successfully, and we could assume unknown or contingent liabilities. It is possible that the integration process could result in the diversion of our management's attention, the disruption or interruption of, or the loss of momentum in, our ongoing business or inconsistencies in standards, controls, procedures and policies, any of which could adversely affect our ability to maintain relationships with third parties or the ability to achieve the anticipated benefits of the acquisition of Xinvento B.V., or could otherwise adversely affect our business and financial results.

We do not anticipate generating revenue from any Xinvento B.V. therapeutic candidate or technology sales for many years.

We do not expect to derive revenue from the sale of any Xinvento B.V. therapeutic candidate or technology for many years and there can be no assurance that regulatory approvals will be received or if received that they will be received when anticipated.

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 information technology 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 information technology systems and those of our third-party CROs, CMOs and other contractors and consultants are vulnerable to attack, damage, or interruption by hacking, cyberattacks, computer viruses and malware (e.g. ransomware), malicious code, phishing attacks and other social engineering schemes, unauthorized access, natural disasters, terrorism, telecommunication and electrical failures, employee theft or misuse, human error, fraud, denial or degradation of service attacks, sophisticated nation-state and nation-state-supported actors or unauthorized access or use by persons inside our organization, or persons with access to systems inside our organization. Any such attack, incident or breach could compromise our information technology systems 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. 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. Even if identified, we may be unable to adequately investigate or remediate incidents or breaches due to attackers increasingly using tools and techniques that are designed to circumvent controls, to avoid detection, and to remove or obfuscate forensic evidence.

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.

We and certain of our service providers have been and from time to time will continue to be subject to cyberattacks and security incidents. While we do not believe that we have experienced any significant system failure, accident or security breach to date, 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. It could also expose us to risks, including an inability to provide our services and fulfill contractual demands, and could cause management distraction and the obligation to devote significant financial and other resources to mitigate such problems, which would increase our future information security costs, including through organizational changes, deploying additional personnel, reinforcing administrative, physical and technical safeguards, further training of employees, changing third-party vendor control practices and engaging third-party subject matter experts and consultants and reduce the demand for our product and services. [We maintain cyber liability insurance; however, this insurance may not be sufficient to cover the financial, legal, business or reputational losses that may result from an interruption or breach of our systems.]

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 10.8% of our outstanding voting stock as of December 31, 2022. 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, 2022, we had approximately $494.5 million and $484.6 million of unused federal and state NOL carryforwards, respectively, and approximately $11.6 million and $3.6 million of unused federal and state carryforwards of research tax credits, respectively. Of the federal NOL carryforwards at December 31, 2022, $421.3 million can be carried forward indefinitely, while $73.2 million will begin to expire in 2033. Additionally, as of December 31, 2022, we had federal orphan drug credits related to qualifying research of $19.3 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, 2022, we had 56,612,429 shares of common stock outstanding.

The holders of an aggregate of approximately 5.0 million shares of our common stock, or approximately 9.0% of our total outstanding common stock as of December 31, 2022, 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 and those subject to lock-up agreements, if applicable.

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 political or 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 economy, including credit and financial markets, has recently experienced extreme volatility and disruptions, including severely diminished liquidity and credit availability, rising interest and inflation rates, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. A severe or prolonged economic downturn or recession and a continued increase in inflation rates or interest rates 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. There can be no assurance that further deterioration in credit and financial markets and confidence in economic conditions will not occur. 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. Increased inflation rates and related increases in interest rates can adversely affect us by increasing our costs, including labor and employee benefit costs. In addition, the current military conflict between Russia and Ukraine could disrupt or otherwise adversely impact our operations and those of third parties upon which we rely. Related sanctions, export controls or other actions have and may in the future be initiated by nations including the U.S., the EU or Russia (e.g., potential cyberattacks, disruption of energy flows, etc.), which could adversely affect our business and/or our supply chain, our CROs, CMOs and other third parties with which we conduct business. 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, 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, once we no longer qualify as a non-accelerated filer or, if before such date, we opt to no longer take advantage of the applicable exemption, we will again be 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, 2023, there were 24 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.

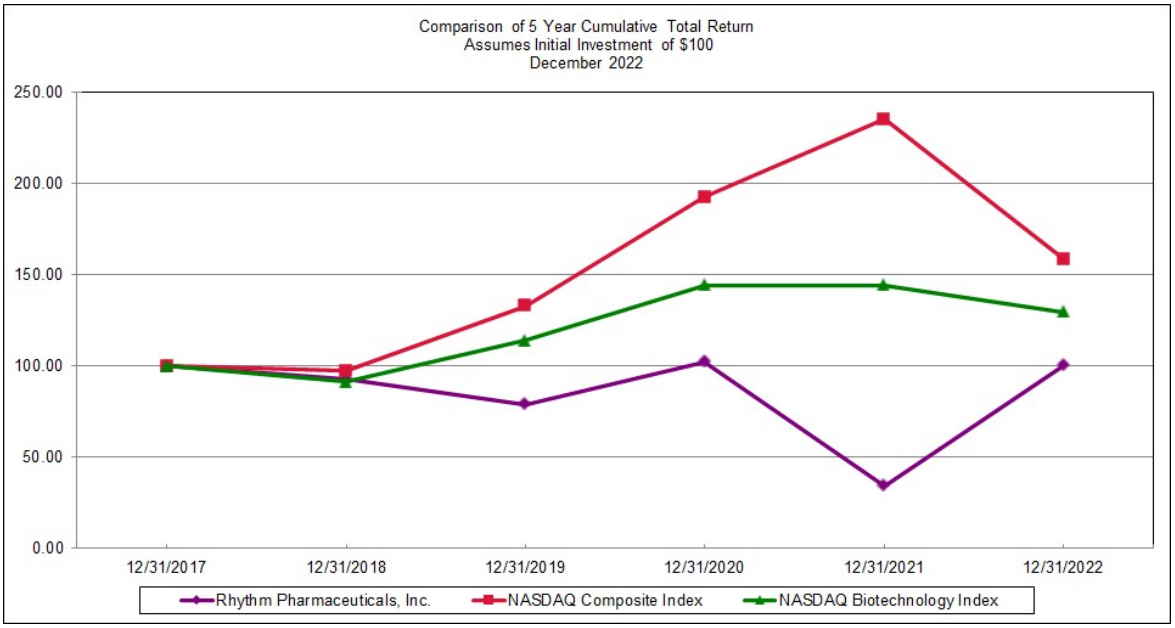
Dividend Policy

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 December 31, 2017 through December 31, 2022 for (1) our common stock, (2) the Nasdaq Composite Index (U.S.) and (3) the Nasdaq Biotechnology Index. Pursuant to applicable SEC 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.

In this Item 7, we discuss the results of operations for the years ended December 31, 2022 and 2021 and comparisons of the year ended December 31, 2022 to the year ended December 31, 2021. Discussion and analysis of our 2020 fiscal year specifically, as well as the year-over-year comparison of our 2021 financial performance to 2020, 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, 2021, filed with the SEC on March 1, 2022.

Overview

We are a global, commercial-stage biopharmaceutical company dedicated to transforming the lives of patients and their families living with rare diseases. We are focused on advancing our lead asset, IMCIVREE® (setmelanotide), as a precision medicine designed to treat hyperphagia and severe obesity caused by rare melanocortin-4 receptor (MC4R) pathway diseases. While obesity affects hundreds of millions of people worldwide, we are advancing IMCIVREE® (setmelanotide) for a subset of individuals who have hyperphagia, a pathological hunger, and severe obesity due to an impaired MC4R pathway, which may be caused by traumatic injury or genetic variants. The MC4R pathway is an endocrine 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 diseases that is approved or authorized in the United States, European Union (EU) and Great Britain. IMCIVREE is approved 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 monogenic or syndromic obesity due to: (i) proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency as determined by an FDA-approved test demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS); or (ii) Bardet-Biedl syndrome (BBS). The European Commission (EC) and Great Britain's Medicines & Healthcare Products Regulatory Agency (MHRA) have authorized IMCIVREE for the treatment of obesity and the control of hunger associated with genetically confirmed BBS or genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. In addition to the United States, we have achieved market access for IMCIVREE for BBS or POMC and LEPR deficiencies, or both, in eight countries outside the United States, and we continue to collaborate with authorities to achieve access in additional markets.

In addition to initial commercial efforts, we are advancing what we believe is the most comprehensive clinical research program ever initiated in MC4R pathway diseases, with multiple ongoing and planned Phase 2 and Phase 3 clinical trials evaluating setmelanotide. We are developing IMCIVREE to address additional patients with acquired hypothalamic obesity and additional MC4R pathway diseases caused by genetic variants in an effort to expand the approved indications and to bring this potential therapy to approximately 53,000 estimated patients in the United States and a similarly-sized patient population in Europe. Following a Phase 2 trial in which 16 of 18 patients with hypothalamic obesity achieved the primary endpoint with a body mass index (BMI) decrease greater than 5 percent on setmelanotide therapy, and in which we observed a 14.5 mean percent reduction in BMI across all patients, we initiated a Phase 3 trial in early 2023. The ongoing pivotal Phase 3 EMANATE trial and Phase 2 DAYBREAK trial are designed to evaluate setmelanotide in several distinct, genetically defined MC4R pathway diseases. We also are conducting a Phase 3 pediatrics trial evaluating daily setmelanotide in patients between the ages of 2 and 6 and a Phase 3 switch trial evaluating a weekly formulation of setmelanotide.

We are leveraging what we believe is the largest known DNA database focused on obesity - with approximately 60,000 sequencing samples as of December 31, 2022 - to improve the understanding, diagnosis and care of people living with severe obesity due to certain variants in genes associated with the MC4R pathway. 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 4,600 to 7,500 for U.S. patients in initial indications, including obesity due to biallelic POMC, PCSK1 or LEPR deficiencies, and BBS. Epidemiology estimates based on our analysis of the literature for patients with hypothalamic obesity is between 5,000 and 10,000 in the United States, and our epidemiology estimates for the indications

being studied in our Phase 3 EMANATE trial suggest that approximately 53,000 U.S. patients with one of these genetically driven obesities have the potential to respond to setmelanotide. 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. Our disease awareness and patient finding efforts are aligned with a singular focus on building a community of caregivers and health care 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 together health care providers, patients and families with educational and awareness events. 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.

On February 27, 2023, we completed the acquisition of Xinvento B.V. (Xinvento), a Netherlands-based biotech company focused on developing therapies for congenital hyperinsulinism (CHI). At closing, Rhythm BV, pursuant to a Share Purchase Agreement, or the Purchase Agreement, with Xinvento, acquired all of the issued and outstanding shares of Xinvento for aggregate consideration of $5 million, as adjusted pursuant to the terms of the Purchase Agreement and subject to the distribution and payment terms set forth therein. In addition, the Purchase Agreement provides for the payment of additional consideration totaling up to $206.0 million upon achievement of certain development, regulatory and commercial milestones by Xinvento. CHI is a rare genetic disease in which cells secrete excess insulin, causing hypoglycemia, which can result in serious health outcomes including seizures, coma, permanent brain damage and death. We plan to expand our pipeline into CHI, a rare disease that is well aligned with our corporate strategy and our focus on rare endocrinology indications. We aim to develop treatment options for these individuals and expect to initiate clinical development of a new therapeutic candidate in 2024. For more information about the acquisition of Xinvento, see Part II, Item 9B. “Other Information.”

On September 19, 2022, the Company completed a public offering of 4,800,000 shares of common stock at a price to the public of $26.00 per share. The Company received $116.9 million in net proceeds after deducting underwriting discounts, commissions and offering expenses. In addition, the Company granted the underwriters a 30-day option to purchase up to an additional 720,000 shares of its common stock at the price to the public, less underwriting discounts and commissions. On October 18, 2022, the Company completed the sale of an additional 580,000 shares of common stock at a price to the public of $26.00 per share pursuant to the partial exercise of the underwriters’ option to purchase additional shares, for aggregate net proceeds of approximately $14.2 million, after deducting underwriting discounts, commissions and offering expenses.

On June 16, 2022, we announced a non-dilutive revenue interest financing agreement, or RIFA, with HealthCare Royalty Partners, LLC, or HealthCare Royalty, for a total investment amount of up to $100 million. In exchange for the total investment amount to be received by Rhythm, HealthCare Royalty will receive a tiered royalty based on global net product sales generated by IMCIVREE. For additional information, see Note 10, “Long-term Obligations” to the consolidated financial statements included elsewhere in this Annual Report.

Our operations to date have been limited primarily to conducting research and development activities for setmelanotide. To date, we have not generated sufficient cash flow from product sales and have financed our operations primarily through the proceeds received from the sales of common and preferred stock, royalty interest financing, 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 October 2022, we have raised aggregate net proceeds of approximately $742.5 million through the issuance of our common stock after deducting underwriting discounts, commissions and offering related transaction costs. We also received $100.0 million from the sale of our Rare Pediatric Disease Priority Review Voucher, or PRV, to Alexion Pharmaceuticals, Inc. in February 2021. In June 2022, we entered into the RIFA with entities managed by HealthCare Royalty Partners and received cumulative proceeds of $73.2 million, net of certain transaction costs at closing. Additionally there is $25.0 million of additional proceeds available to us under our RIFA if certain sales based milestone is achieved during 2023. In December 2021, we entered into an Exclusive License Agreement with RareStone Group Ltd., or RareStone, and received $7.0 million from the execution of that agreement.

We have built a US marketing and commercialization infrastructure to support our U.S. launch of IMCIVREE, and are building a comparable infrastructure in Canada and certain European countries as we achieve approval and reimbursement authorization. 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. We launched IMCIVREE for patients 6 years of age and older with obesity due to BBS during June 2022. Following marketing authorizations in the EU and Great Britain, we are pursuing a country-by-country strategy to establish market access and reimbursement for IMCIVREE in several countries. During March 2022, we treated the first patients with IMCIVREE in France under the paid early access program and we treated the first patients with IMCIVREE in Germany during June 2022. Additionally, we have treated our initial patients in the United Kingdom, Italy, The Netherlands and Turkey during the fourth quarter of 2022. We expect to continue to fund our operations through the sale of equity, debt financings or other sources. We intend to build our own marketing and commercial sales infrastructure and we may enter into collaborations with other parties for certain markets outside the United States. However, we may be unable to raise additional funds or enter into such other arrangements when needed on favorable terms, or at all. If we fail to raise capital or enter into such other arrangements as, and when, needed, we may have to significantly delay, scale back or discontinue the development or commercialization of setmelanotide.

As of December 31, 2022 we had an accumulated deficit of $710.1 million. Our net losses were $181.1 million and $69.6 million, for the years ended December 31, 2022 and 2021, 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, 2022, our cash and cash equivalents and short-term investments were approximately $333.3 million. We expect that our cash and cash equivalents and short-term investments as of December 31, 2022, will enable us to fund our operating expenses into 2025.

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 COVID-19

We are monitoring the continued impact of COVID-19 on our employees, business, preclinical studies and clinical trials. 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. In 2020, 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, evolving 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 generated less than $25.0 million of 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 United States in the first quarter of 2021. We recorded our first sales of IMCIVREE in the United States in March 2021 and we made our first sales in France in March 2022 under the paid early access program. IMCIVREE was approval by the FDA and the EC in adult and pediatric patients six years of age and older with obesity due to BBS in June and September 2022, respectively. Following these approvals for BBS, we expect our sales of IMCIVREE will continue to grow as we identify and treat more patients with this disease and obtain reimbursement throughout the international markets in which we operate.

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, 2022 were insignificant. We expect cost of sales to increase in 2023 as we have begun to sell inventory produced after we began capitalizing manufacturing costs for IMCIVREE commercial inventory. We continue to evaluate the impact of this previously expensed inventory on the future cost of product sales, however we do not expect there to be a significant impact based on the cost structure of the product.

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	**2022**	**2021**
Research and development expense	$ 108,630	$ 104,128

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 commercialization of setmelanotide as well as salaries and related benefits for commercial employees, including stock-based compensation. As we further implement and execute our commercialization plans to market setmelanotide in new territories 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, 2022	2021
Selling, general and administrative expense	$ 92,032	$ 68,486

We anticipate that our selling, general and administrative expenses will increase in the future to support continued and expanding commercialization efforts for IMCIVREE in the United States and the European Union 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 local rules and regulations in the United States and foreign jurisdictions, 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 maintain the Rhythm Pharmaceuticals, Inc. 2017 Equity Incentive Plan, (the "2017 Plan") which provides for the grant of incentive stock options, non-qualified stock options, stock appreciation rights, performance units, restricted stock awards, restricted stock units and stock grants to employees, consultants, advisors and directors, as determined by the board of directors. As of December 31, 2022, we had reserved 10,149,772 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.

On February 9, 2022, our board of directors adopted the Rhythm Pharmaceuticals, Inc. 2022 Employment Inducement Plan (the "2022 Inducement Plan"), which became effective on such date without stockholder approval pursuant to Rule 5635(c)(4) of the Nasdaq Stock Market LLC listing rules ("Rule 5635(c)(4)"). The 2022 Inducement Plan provides for the grant of non-qualified stock options, stock appreciation rights, performance units, restricted stock awards, restricted stock units and stock grants. In accordance with Rule 5635(c)(4), awards under the 2022 Inducement Plan may only be made to a newly hired employee who has not previously been a member of our 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 our common stock have been reserved for issuance under the 2022 Inducement Plan.

The exercise price of stock options granted under the 2022 Inducement Plan will not be less than the fair market value of a share of our common stock on the grant date. Other terms of awards, including vesting requirements, are determined by our board of directors and are subject to the provisions of the 2022 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 2022 Inducement Plan expire no more than 10 years from the date of grant. As of December 31, 2022, there were 336,780 stock option awards outstanding, 173,135 restricted stock unit awards outstanding and 490,085 shares of common stock available for future grant under the 2022 Inducement Plan.

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. 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 previously 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 computed 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, 2022, 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, 2022, we had net operating loss carryforwards to reduce federal and state incomes taxes of approximately $494.5 million and $484.6 million, respectively. If not utilized, these carryforwards begin to expire in 2033. Of the federal net operating loss carryforwards at December 31, 2022, $421.3 million can be carried forward indefinitely. At December 31, 2022, we also had available research and development tax credits for federal and state income tax purposes of approximately $11.6 million and $3.6 million, respectively. Additionally, as of December 31, 2022, we had federal orphan drug credits related to qualifying research of $19.3 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, 2022 and 2021

The following table summarizes our results of operations for the years ended December 31, 2022 and 2021, together with the changes in those items in dollars and as a percentage:

	Year Ended December 31,		Change	
	2022	2021	$	%
	(in thousands)			
Statement of Operations Data:				
Revenues:				
Product revenue, net	$ 16,884	$ 3,154	$ 13,730	435 %
License revenue	6,754	—	6,754	NM
Total revenues	23,638	3,154	20,484	649 %
Costs and expenses:				
Cost of sales	2,133	599	1,534	256 %
Research and development	108,630	104,128	4,502	4 %
Selling, general, and administrative	92,032	68,486	23,546	34 %
Total costs and expenses	202,795	173,213	29,582	17 %
Loss from operations	(179,157)	(170,059)	(9,098)	5 %
Other (expense) income, net	(1,962)	100,447	(102,409)	(102)%
Net loss	$ (181,119)	$ (69,612)	$ (111,507)	160 %

NM=Not meaningful

Product revenue, net increased by $13.7 million to $16.9 million in 2022 from $3.2 million in 2021 an increase of 435%. We recorded our first sales of IMCIVREE in March 2021 and the year ended December 31, 2021 represented our first year of sales subsequent to the approval of IMCIVREE in November 2020. We expect our sales of IMCIVREE to continue to increase following the FDA approval for the treatment of patients with BBS in the United States during June 2022 and by the EC in September 2022. For the years ended December 31, 2022 and 2021, 85% and 100%, respectively, of our product revenue was generated in the United States.

License revenue. License revenue was $6.8 million in 2022 and was entirely related to the RareStone license agreement. We entered into a license agreement with RareStone in December 2021 and completed our activities required to transfer the license to RareStone during the second quarter of 2022, which resulted in the recognition of the license revenue.

Cost of sales. Cost of sales increased by $1.5 million to $2.1 million in 2022 from $0.6 million in 2021, an increase of 256%. Most of the IMCIVREE manufacturing costs have been recorded as research and development expenses in prior periods. Accordingly, the product cost component related for IMCIVREE included in our cost of sales for the year ended December 31, 2022 was insignificant and cost of sales primarily reflects a royalty due to Ipsen Pharma S.A.S., or Ipsen, on our net product sales and the amortization of our capitalized sales based milestone payment made to Ipsen, upon our first commercial sale in the U.S.and EU. Specifically, the $1.5 million increase in cost of sales for the year ended December 31, 2022 was due to $0.7 million of additional royalties due to our growth in sales, $0.5 million attributed to product cost primarily associated with higher sales volume and product distributed four our patient assistance program, and $0.3 million of additional amortization. We expect cost of sales to increase overtime as we sell inventory that is produced after we began capitalizing IMCIVREE commercial inventory.

Research and development expense. Research and development expense increased by $4.5 million to $108.6 million in 2022 from $104.1 million in 2021, an increase of 4%. The increase was primarily due to the following:

- an increase of $2.9 million due to increased purchases of clinical supply material;

- an increase of $2.8 million in gene sequencing costs to support our expanded clinical programs;

- an increase of $2.4 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, Phase 2 hypothalamic obesity study, Phase 3 hypothalamic obesity study and increased enrollment in our long-term extension and switch trial. These increases were partially offset by reduced activity due to the completion and winding down of our Phase 3 POMC and LEPR trials, QTc trial, BBS trial, Phase 2 Basket trial and our renal study. These increases were further offset by a $2.3 million refund due to us upon the close out and reconciliation of the GO-ID study, all of which resulted in an insignificant change in our clinical trial expense;

- an increase of $2.1 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;

- an increase of $1.0 million in development milestones earned by Camurus AB, or Camurus, related to development milestone achieved related to our weekly formulation; and

- an increase of $0.9 million related to IP and patent related filing activities.

The above increases were partially offset by:

- a decrease of $4.0 million in costs associated with medical affairs; and

- a decrease of $0.9 million in costs associated with next generation research and development activities.

Selling, general and administrative expense. Selling, general and administrative expense increased by $23.5 million to $92.0 million in 2022 from $68.5 million in 2021, an increase of 34%. The increase was primarily due to the following:

- an increase of $9.6 million due to increased compensation and benefits related costs associated with additional headcount to support our expanding business operations as well as to establish commercial operations in the United States and internationally;

- an increase of $8.6 million related to increased costs associated with commercial operations, sales and marketing activities for IMCIVREE in connection with preparing for the U.S. approval for BBS obtained in June 2022 and EC approval in September 2022;

- an increase of $5.0 million due to increased costs associated with information technology, international office space, sponsorships and general corporate travel related expenses for our expanding workforce.

Other (expense) income, net. Other (expense) income, net decreased by $102.4 million to ($2.0) million in 2022, a decrease of 102%. The decrease was primarily due to the sale of our PRV in February 2021. The sale of our PRV in the prior year was a non-recurring transaction, which resulted in $100.0 million of other income during the prior year. Other (expense) income, net consists of $5.2 million of interest expense related to our RIFA (including amortization of debt discount and deferred financing fees) and a $1.0 million other than temporary impairment of our RareStone equity, partially offset by $4.0 million of interest income and $0.3 million of other income resulting from the remeasurement of our embedded derivative related to our RIFA.

Net loss. Net loss increased by $111.5 million to $181.1 million in 2022, from net loss of $69.6 million in 2021. The increase in net loss was primarily a result of the non-recurring nature of our PRV sale in 2021, which resulted in $100.0 million of other income during the prior year , as well as higher costs as discussed above partially offset by product and license revenue in the current year as noted above.

Liquidity and Capital Resources

As of December 31, 2022, our cash and cash equivalents and short-term investments were approximately $333.3 million.

Cash flows

The following table provides information regarding our cash flows for the years ended December 31, 2022 and 2021:

	Year Ended December 31,	
	2022	2021
	(in thousands)	
Net cash provided by (used in):		
Operating activities	$ (173,428)	$ (146,003)
Investing activities	28,029	(62,159)
Financing activities	213,828	166,481
Net increase (decrease) in cash, cash equivalents and restricted cash	$ 68,429	(41,681)

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 $173.4 million for the year ended December 31, 2022, and consisted primarily of a net loss of $153.7 million adjusted for non-cash items, which consisted of stock-based compensation, depreciation and amortization, non-cash rent expense, the change in the fair value of our embedded derrivative liability, and the impairment of RareStone equity. The change in operating assets and liabilities reflected a total use of cash of approximately $19.7 million primarily driven by a decrease of $14.7 million in accounts receivable, inventory, prepaid expenses, other current and other long term assets coupled with a decrease in accounts payable, accrued expenses, and deferred revenue of $5.1 million due to the timing of payments.

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 provided by (used in) investing activities

Net cash provided by investing activities was $28.0 million for the year ended December 31, 2022 which relates to the proceeds from short-term investments of $32.2 million, partially offset by $0.3 million related to the purchase of property plant and equipment and $4.0 million for the acquisition of an intangible asset.

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 financing activities

Net cash provided by financing activities was $213.8 million for the year ended December 31, 2022, which represents the net proceeds of $131.1 million from our common stock offering in September 2022, $72.3 million of aggregate proceeds, net of issuance costs from the RIFA, and $10.4 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 $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 2022 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.

Revenue Interest Financing Agreement

On June 16, 2022, we entered into the RIFA, with HealthCare Royalty, for a total investment amount of up to $100 million. In exchange for the total investment amount to be received by Rhythm, HealthCare Royalty will receive a tiered royalty based on global net product sales generated by IMCIVREE. For additional information, see Note 10, “Long-term Obligations” to the consolidated financial statements included elsewhere in this Annual Report.

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, and build out our global organization. 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. As a result of the acquisition of Xinvento, we expect to devote substantial financial resources to the research and development and potential commercialization of a therapeutic product candidate for CHI.

We expect that our $333.3 million of cash and cash equivalents and short-term investments as of December 31, 2022, will enable us to fund our operating expenses into 2025. 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 costs related to the acquisition, integration, research and development and commercialization efforts related to the acquisition of Xinvento B.V. and any related therapeutic product candidates;
- the obligations owed to Ipsen, Camurus and Takeda Pharmaceutical Company Limited, or 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 COVID-19” 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.

Further, the global economy, including credit and financial markets, has recently experienced extreme volatility and disruptions, including severely diminished liquidity and credit availability, rising interest and inflation rates, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. All of these factors could impact our liquidity and future funding requirements, including but not limited to our ability to raise additional capital when needed on acceptable terms, if at all. The duration of this economic slowdown is uncertain and the impact on our business is difficult to predict. See “Risk Factors— Unfavorable global political or economic conditions could adversely affect our business, financial condition or results of operations.”

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, 2022 there were $27.0 million of remaining milestones that may be achieved and due to Ipsen at a future date. During 2022, we paid Ipsen a $4.0 million milestone upon our first commercial sale of IMCIVREE in Europe. We do not expect to make additional milestone payments to Ipsen during 2023. 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 the weekly formulation of 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, 2022 there were $62.5 million of remaining milestones that may be achieved and due to Camurus at a future date. We paid Camurus a $1.0 million milestone in 2022 upon the achievement of a development milestone. We do not expect to make any milestone payments to Camurus during 2023. 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 weekly 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. We have notified Takeda that we have halted development activities related to RM-853. We do not expect to make milestone payments to Takeda during 2023 or for the foreseeable future.

Based on our current development plans as of December 31, 2022, we do not expect to make payments to third parties, during the next 12 months from the filing of this Annual Report. 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, 2022, 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, 2022. 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, 2022.

Attestation Report of the Registered Public Accounting Firm

This Annual Report does not include an attestation report of our independent registered public accounting firm in reliance on the exemption from such requirement available to non-accelerated filers.

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 2022 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Click or tap here to enter text.

Item 9B. Other Information

On February 27, 2023, the Company, through its wholly-owned Dutch subsidiary, Rhythm Pharmaceuticals Netherlands B.V., a Dutch private limited liability company ("Rhythm BV"), entered into a Share Purchase Agreement (the "Purchase Agreement") with Xinvento B.V., a Dutch private limited liability company based in the Netherlands

("Xinvento"), and the other parties named therein, pursuant to which, and concurrently with the execution thereof, Rhythm BV acquired all of the issued and outstanding shares of Xinvento for aggregate consideration at closing of $5 million, as adjusted pursuant to the terms of the Purchase Agreement and subject to the distribution and payment terms set forth therein (the "Closing Purchase Price").

In addition to the Closing Purchase Price, the Purchase Agreement provides for the payment of additional consideration totaling up to $206.0 million upon achievement of certain development, regulatory and commercial milestones by Xinvento, as follows: (i) up to an aggregate of $6.0 million in clinical development milestones; (ii) up to an aggregate of $125.0 million in regulatory approval and commercial milestones; and (iii) up to an aggregate of $75.0 million in sales milestones in the event a second molecule is selected, developed and approved.

The Purchase Agreement contains customary representations, warranties and covenants, including covenants by Sellers (as defined in the Purchase Agreement) to indemnify Rhythm BV and certain related parties for breaches of certain representations, warranties and covenants in the Purchase Agreement, subject to customary exclusions and caps. The representations and warranties contained in the Purchase Agreement have been made for the benefit of the other parties thereto and should not be relied upon by any other person. Such representations and warranties (i) have been qualified by schedules and exhibits, (ii) are subject to materiality standards that may differ from what may be viewed as material by investors, (iii) are made as of specified dates, and (iv) may have been used for the purpose of allocating risk among the parties rather than establishing matters of fact. Accordingly, the representations and warranties should not be relied upon as characterizations of the actual state of facts.

The foregoing description of the Purchase Agreement is not complete and is qualified in its entirety by reference to the full text of the Purchase Agreement, a copy of which is filed herewith as Exhibit 2.2 and incorporated by reference herein.

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 2023 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, 2022.

Item 11. Executive Compensation

The information required under this item is incorporated herein by reference to our definitive proxy statement for our 2023 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, 2022.

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, 2022, regarding our common stock that may be issued under (1) the 2017 Plan; (2) our 2017 Employee Stock Purchase Plan, (the 2017 ESPP); and (3) the 2022 Inducement Plan.

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 (6)**	**Number of Securities Available for Future Issuance Under Equity Compensation Plans**
Equity compensation plans approved by stockholders				
2017 Plan (1)	7,443,592	(4)	$ 17.81	2,726,180
2017 ESPP (2)	—		—	1,372,845
Equity compensation plans not approved by stockholders	—		—	—
2022 Inducement Plan (3)	509,915	(5)	19.33	490,085
Total	7,953,507		$ 17.89	4,589,110

(1) The 2017 Plan provides for an annual increase on each January 1 commencing in 2018 and ending in 2027, 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 in 2018 and ending in 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.

(3) The 2022 Inducement Plan adopted on February 9, 2022. Awards issued under the 2022 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 were reserved for issuance under the 2022 Inducement Plan. The material terms of the 2022 Inducement Plan are described in Note 8 to the consolidated financial statements included herein.

(4) Includes 6,037,764 outstanding options to purchase shares of common stock, 601,031 outstanding restricted stock units and 804,797 outstanding performance share units.

(5) Includes 336,780 outstanding options to purchase shares of common stock and 173,135 outstanding restricted stock units.

(6) Restricted stock units have no exercise price and are not taken into account when calculating weighted average exercise price.

Other

The remaining information required under this item is incorporated herein by reference to our definitive proxy statement for our 2023 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, 2022.

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 2023 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, 2022.

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 2023 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, 2022.

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
2.2*	Share Purchase Agreement, by and between Rhythm Pharmaceuticals Netherlands B.V. and Xinvento B.V., dated February 27, 2023.			
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	Form of Indenture to be entered into between the Registrant and a trustee acceptable to the registrant.	S-3	11/2/2021	4.3
4.3*	Description of the Registrant's Securities registered pursuant to Section 12 of the Securities Exchange Act of 1934.			
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-K	3/1/2022	10.5.1
10.5.2†	2022 Employment Inducement Plan Form of Restricted Stock Unit Agreement	10-K	3/1/2022	10.5.2
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-K	3/1/2022	10.10
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 June 23, 2020, by and between the Registrant and Joseph Shulman.			
10.21†	Offer Letter, dated September 25, 2020, by and between the Registrant and Jennifer Chien.	10-K	3/1/2021	10.16
10.22†	Offer Letter, dated July 16, 2020, by and between the Registrant and David P. Meeker, M.D.	8-K	7/21/2020	10.1
10.23†	Offer Letter, dated July 9, 2021, by and between the Registrant and Pamela Cramer	10-Q	8/03/2021	10.1
10.24††	Revenue Interest Financing Agreement, dated June 16, 2022, by and between the Company and entities managed by HealthCare Royalty Management, LLC	10-Q	8/03/2022	10.1
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, 2023
/s/ Hunter Smith Hunter Smith	Chief Financial Officer (Principal Financial Officer)	March 1, 2023
/s/ William T. Roberts William T. Roberts	Chief Accounting Officer (Principal Accounting Officer)	March 1, 2023
/s/ Edward T. Mathers Edward T. Mathers	Lead Director	March 1, 2023
/s/ Stuart Arbuckle Stuart Arbuckle	Director	March 1, 2023
/s/ Camille L. Bedrosian, M.D. Camille L. Bedrosian M.D.	Director	March 1, 2023
/s/ Jennifer L. Good Jennifer L. Good	Director	March 1, 2023
/s/ Christophe R. Jean Christophe R. Jean	Director	March 1, 2023
/s/ David W. J. McGirr David W. J. McGirr	Director	March 1, 2023
/s/ Lynn A. Tetrault Lynn A. Tetrault	Director	March 1, 2023

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, 2022 and 2021, 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, 2022, 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, 2022 and 2021, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2022, in conformity with U.S. generally accepted accounting principles.

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. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits, we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

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 $32.9 million at December 31, 2022, which included the estimated obligation for research and development expenses incurred as of December 31, 2022 but not paid as of that date. In addition, the Company's total prepaid expenses and other current assets were $11.8 million and other long-term assets were $16.7 million at December 31, 2022, 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, 2022 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, 2023

RHYTHM PHARMACEUTICALS, INC.

CONSOLIDATED BALANCE SHEETS

(in thousands, except share and per share data)

	December 31, 2022	December 31, 2021
Assets		
Current assets:		
Cash and cash equivalents	$ 127,677	$ 59,248
Short-term investments	205,611	235,607
Accounts receivable, net	6,224	1,025
Inventory	2,917	111
Prepaid expenses and other current assets	11,807	12,396
Total current assets	354,236	308,387
Property and equipment, net	2,197	2,813
Right-of-use asset	1,182	1,522
Intangible assets, net	7,883	4,658
Restricted cash	328	328
Other long-term assets	16,655	11,815
Total assets	$ 382,481	$ 329,523
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 4,797	$ 5,737
Accrued expenses and other current liabilities	32,894	30,084
Deferred revenue	1,434	7,000
Lease liability	684	606
Total current liabilities	39,809	43,427
Long-term liabilities:		
Deferred royalty obligation	75,810	—
Lease liability	1,260	1,945
Derivative liability	1,340	—
Total liabilities	118,219	45,372
Commitments and contingencies (Note 11)		
Stockholders' equity:		
Preferred stock, $0.001 par value: 10,000,000 shares authorized; no shares issued and outstanding at December 31, 2022 and December 31, 2021	—	—
Common stock, $0.001 par value: 120,000,000 shares authorized; 56,612,429 and 50,283,574 shares issued and outstanding at December 31, 2022 and December 31, 2021, respectively	56	50
Additional paid-in capital	974,356	813,041
Accumulated other comprehensive loss	(92)	(1)
Accumulated deficit	(710,058)	(528,939)
Total stockholders' equity	264,262	284,151
Total liabilities and stockholders' equity	$ 382,481	$ 329,523

The accompanying notes are an integral part of these financial statements

RHYTHM PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS

(in thousands, except share and per share data)

	Year Ended December 31, 2022	Year Ended December 31, 2021	Year Ended December 31, 2020
Revenues:			
Product revenue, net	$ 16,884	$ 3,154	$ —
License revenue	6,754	—	—
Total revenues	23,638	3,154	—
Costs and expenses:			
Cost of sales	2,133	599	—
Research and development	108,630	104,128	90,450
Selling, general, and administrative	92,032	68,486	46,125
Total costs and expenses	202,795	173,213	136,575
Loss from operations	(179,157)	(170,059)	(136,575)
Other income:			
Other (expense), income, net	(790)	100,000	—
Interest expense	(5,201)	—	—
Interest income	4,029	447	2,579
Total other (expense) income, net	(1,962)	100,447	2,579
Net loss	$ (181,119)	$ (69,612)	$ (133,996)
Net loss per share, basic and diluted	(3.47)	(1.40)	(3.04)
Weighted-average common shares outstanding, basic and diluted	52,120,701	49,600,294	44,127,220
Other comprehensive loss:			
Net loss	$ (181,119)	$ (69,612)	$ (133,996)
Unrealized (loss) gain, net on marketable securities	(91)	(1)	49
Comprehensive loss	$ (181,210)	$ (69,613)	$ (133,947)

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, 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
Issuance of common stock upon completion of public offering, net of offering costs	—	—	—	—	—	—
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
Change in 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
Stock compensation expense	—	—	19,831	—	—	19,831
Issuance of common stock in connection with ESPP	92,932	—	626	—	—	626
Issuance of common stock in connection with exercise of stock options and vesting of restricted stock units	855,923	1	9,751	—	—	9,752
Issuance of common stock upon completion of public offering, net of offering costs	5,380,000	5	131,107	—	—	131,112
Unrealized loss on marketable securities	—	—	—	(91)	—	(91)
Net loss	—	—	—	—	(181,119)	(181,119)
Balance at December 31, 2022	56,612,429	$ 56	$ 974,356	$ (92)	$ (710,058)	$ 264,262

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,		
	2022	2021	2020
Operating activities			
Net loss	$ (181,119)	$ (69,612)	$ (133,996)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation expense	19,831	20,804	17,455
Gain on sale of priority review voucher	—	(100,000)	—
Depreciation and amortization	1,672	1,158	690
Non-cash interest expense and amortization of debt issuance costs	5,389	—	—
Non-cash rent expense	(267)	(250)	(234)
Loss on RareStone equity investment	1,040	—	—
Change in fair value of embedded derivative liability	(250)	—	—
Changes in operating assets and liabilities:			
Accounts receivable	(5,199)	(1,250)	
Inventory	(2,806)	(11)	
Prepaid expenses and other current assets	(1,816)	(3,339)	551
Deferred revenue	(6,606)	—	—
Other long-term assets	(4,840)	(11,815)	—
Accounts payable, accrued expenses and other current liabilities	1,543	18,312	(6,446)
Net cash used in operating activities	(173,428)	(146,003)	(121,980)
Investing activities			
Purchases of short-term investments	(251,937)	(524,972)	(86,869)
Maturities of short-term investments	284,247	361,247	245,614
Proceeds from sale of priority review voucher	—	100,000	—
Proceeds from out-license agreement	—	7,000	—
Payment of milestone obligation under license agreement	(4,000)	(5,000)	—
Purchases of property and equipment	(281)	(434)	(214)
Net cash provided by (used in) investing activities	28,029	(62,159)	158,531
Financing activities			
Net proceeds from issuance of common stock	131,112	161,726	—
Proceeds from the exercise of stock options	9,752	4,134	1,487
Proceeds from issuance of common stock from ESPP	626	621	522
Proceeds from royalty financing agreement, net of issuance costs	72,338	—	—
Net cash provided by financing activities	213,828	166,481	2,009
Net increase (decrease) in cash, cash equivalents and restricted cash	68,429	(41,681)	38,560
Cash, cash equivalents and restricted cash at beginning of period	59,576	101,257	62,697
Cash, cash equivalents and restricted cash at end of period	$ 128,005	$ 59,576	$ 101,257

The accompanying notes are an integral part of these financial statements

Rhythm Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements

(In thousands, except share and per share information)

1. Nature of Business

Rhythm Pharmaceuticals, Inc. (the "Company" or "we") is a global, commercial-stage biopharmaceutical company dedicated to transforming the lives of patients and their families living with rare diseases. We are focused on advancing our lead asset, IMCIVREE® (setmelanotide), as a precision medicine designed to treat hyperphagia and severe obesity caused by rare melanocortin-4 receptor (MC4R) pathway diseases. While obesity affects hundreds of millions of people worldwide, we are advancing IMCIVREE® (setmelanotide) for a subset of individuals who have hyperphagia, a pathological hunger, and severe obesity due to an impaired MC4R pathway, which may be caused by traumatic injury or genetic variants. The MC4R pathway is an endocrine 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 diseases that is approved or authorized in the United States, European Union (EU) and Great Britain.

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 Kingdom, the Netherlands, France, Germany, Italy, Spain and Canada.

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 sufficient revenue from product sales to fund operations.

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 year ended December 31, 2022, 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, 2022, the Company had an accumulated deficit of $710,058. The Company has primarily funded these losses through the proceeds from the sales of common and preferred stock, royalty financing, 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, commercialization activities and general and administrative functions relating to these operations. The future success of the Company is dependent on its ability to develop its product candidates and ultimately upon its ability to attain profitable operations.

At December 31, 2022, the Company had $333,288 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”).

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 estimates related to determining our net product revenue, license revenue, accruals related to research and development expenses, assumptions used to record stock-based compensation expense, interest expense on our deferred royalty obligation, assumptions used to value the embedded derivative in our deferred royalty obligation, assumptions used to value the common stock received from RareStone Group Ltd., or RareStone, 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.

Reclassification of Prior Year Balances

Certain prior year amounts have been reclassified to conform to the current period presentation. These reclassifications had no effect on the reported results of operations or cash flows. Specifically, in the consolidated balance sheet as of December 31, 2021, the Company has reclassified $111 which was previously recorded within prepaid expenses and other current assets to inventory. Additionally, in the consolidated statement of cash flows for the year ended December 31, 2021, the Company has reclassified $1,025 and $111 due to the effects of changes in the accounts receivable and

inventory, respectively, from changes in prepaid expenses and other current assets to changes in accounts receivable of and inventory, respectively.

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. For the year ended December 31, 2022, approximately 85% of all of the Company's revenue was generated from a single customer in the United States. For the year ended 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.

The Company relies on separate third-parties to perform genetic testing in the United States and Europe, respectively. The inability of the vendor to fulfill testing services for the Company could materially impact future operating results and adversely impact our ability to further develop setmelanotide. A change in the relationship with the genetic testing service providers, 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, 2022, 2021, and 2020, the Company did not recognize any credit losses related to its available-for-sale debt securities. Further, as of December 31, 2022 and 2021, 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 contracts with its customers have customary payment terms that generally require payment within 90 days. The Company analyzes amounts that are past due for collectability, and periodically evaluates the creditworthiness of its customer. At December 31, 2022 and 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

In the United States (the "U.S."), which accounts for the largest portion of our total revenues, the Company sells its product to a limited number of specialty pharmacies. The product is distributed through third-party logistics, or 3PL, distribution agent that does not take title to the product. Once the product is delivered to the Company's specialty pharmacy provider, our customer in the U.S., the customer (or "wholesaler") takes title to the product. The wholesaler then distributes the product to patients. In our distribution agreement with the 3PL company, the Company acts as principal because we retain control of the product. Internationally, we make sales primarily to specialty distributors and retail pharmacy chains, as well as hospitals, many of which are government-owned or supported. The Company generally does not offer returns of product sold to the customer.

Revenue from product sales is 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 customers 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 and comprehensive (loss) income. 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 ninety days or less, the Company concluded 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 customers, 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 customers. The government and other entities charge us for the difference between what they pay for the product and the selling price to our customers. The Company records reserves for these chargebacks related to product sold to our customers 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 as well as certain government rebates and pricing adjustments in certain international markets that we operate. 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 and other current liabilities on our consolidated balance sheets. 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 certain of our customers 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 customers 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 customers have 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.

The table below summarizes balances and activity in each of the product revenue allowance and reserve categories as follows:

	Provision for Cash Discounts	Fees, Rebates and Other Incentives	Total
Beginning Balance at December 31, 2020	$ —	$ —	$ —
Provision related to sales in the current year	74	495	569
Credit and payments made	(53)	(42)	(95)
Ending balance December 31, 2021	$ 21	$ 453	$ 474
Provision related to sales in the current year	367	3,299	3,666
Credit and payments made	(289)	(1,042)	(1,331)
Ending balance December 31, 2022	$ 99	$ 2,710	$ 2,809

Provision for cash discounts are recorded as reductions of accounts receivable, and fees, rebates, and other incentives are recorded as a component of accrued expenses.

License Agreements

We generate revenue from license or similar agreements with pharmaceutical companies for the development and commercialization of certain of our products and product candidates. Such agreements may include the transfer of intellectual property rights in the form of licenses, transfer of technological know-how, delivery of drug substances, research and development services, and participation on certain committees with the counterparty. Payments made by the customers may include non-refundable upfront fees, payments upon the exercise of customer options, payments based upon the achievement of defined milestones, and royalties on sales of products and product candidates if they are approved and commercialized.

If a license to our intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, we recognize the transaction price allocated to the license as revenue upon transfer of control of the license. We evaluate all other promised goods or services in the agreement to determine if they are distinct. If they are not distinct, they are combined with other promised goods or services to create a bundle of promised goods or services that is distinct. Optional future services where any additional consideration paid to us reflects their standalone selling prices do not provide the customer with a material right and, therefore, are not considered performance obligations. If optional future services are priced in a manner which provides the customer with a significant or incremental discount, they are material rights, and are accounted for as separate performance obligations.

We utilize judgment to determine the transaction price. In connection therewith, we evaluate contingent milestones at contract inception to estimate the amount which is not probable of a material reversal to include in the transaction price using the most likely amount method. Milestone payments that are not within our control, such as regulatory approvals, are not considered probable of being achieved until those approvals are received and therefore the variable consideration is constrained. The transaction price is then allocated to each performance obligation on a relative stand-alone selling price basis, for which we recognize revenue as or when the performance obligations under the contract are satisfied. At the end of each reporting period, we re-evaluate the probability of achieving development milestone payments that may not be subject to a material reversal and, if necessary, adjust our estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect license and other revenue, as well as earnings, in the period of adjustment.

We then determine whether the performance obligations or combined performance obligations are satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue from non-refundable, upfront fees. We evaluate the measure of progress, as applicable, for each reporting period and, if necessary, adjust the measure of performance and related revenue recognition.

When consideration is received, or such consideration is unconditionally due, from a customer prior to transferring goods or services to the customer under the terms of a contract, a contract liability is recorded within deferred revenue. Contract liabilities within deferred revenue are recognized as revenue after control of the goods or services is transferred to the customer and all revenue recognition criteria have been met.

For arrangements that include sales-based royalties, including sales-based milestone payments, and a license of intellectual property that is deemed to be the predominant item to which the royalties relate, we recognize revenue at the later of when the related sales occur or when the performance obligation to which some or all of the royalties have been allocated has been satisfied (or partially satisfied). Refer to Note 9 “Significant Agreements”, for discussion related to the Company’s accounting for the RareStone Group, Ltd. agreement.

Deferred Royalty Obligation

We treat the debt obligation to HealthCare Royalty Management, LLC as discussed further in Note 10, “Long-term Obligations”, as a deferred royalty obligation, amortized using the effective interest rate method over the estimated life of the revenue streams. We recognize interest expense thereon using the effective rate, which is based on our current estimates of future revenues over the life of the arrangement. In connection therewith, we periodically assess our expected revenues using internal projections, impute interest on the carrying value of the deferred royalty obligation, and record interest expense using the imputed effective interest rate. To the extent our estimates of future revenues are greater or less than previous estimates or the estimated timing of such payments is materially different than previous estimates, we will account for any such changes by adjusting the effective interest rate on a prospective basis, with a corresponding impact to the reclassification of our deferred royalty obligation. The assumptions used in determining the expected repayment term of the deferred royalty obligation and amortization period of the issuance costs requires that we make estimates that could impact the classification of such costs, as well as the period over which such costs will be amortized.

Inventory

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. In connection therewith, the Company values inventories at the lower of cost or estimated net realizable value. The Company determines the cost of inventories, which includes amounts related to materials and manufacturing overhead, on a first-in, first-out basis. Raw materials and work in process includes all inventory costs prior to packaging and labelling, including raw materials, active pharmaceutical ingredient, and drug product. Finished goods include packaged and labelled products. Raw materials and work in process that may be used for either research and development or commercial sale are classified as inventory until the material is consumed or otherwise allocated for research and development. If the material is intended to be used for research and development, it is expensed as research and development once that determination is made.

Inventory consists of the following:

	December 31, 2022	December 31, 2021
Raw Materials	$ 2,722	$ —
WIP	—	—
Finished Goods	195	111
Total Inventory	$ 2,917	$ 111

Cost of Product Sales

Cost of product sales consists of manufacturing costs, transportation and freight, amortization of capitalized intangibles, royalty payments and indirect overhead costs associated with the manufacturing and distribution of IMCIVREE. Cost of product sales may also include periodic costs related to certain manufacturing services and inventory

adjustment charges. Finally, cost of sales may also include costs related to excess or obsolete inventory adjustment charges, abnormal costs, unabsorbed manufacturing and overhead costs, and manufacturing variances.

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 comparing 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, 2022, 2021 and 2020.

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,	
	2022	2021
Prepaid research and development costs	$ 4,392	$ 8,404
Other current assets	7,415	3,992
Prepaid expenses and other current assets	$ 11,807	$ 12,396

Property and Equipment

Property and equipment consists of the following:

	Useful Life	December 31,	
		2022	2021
Leasehold improvements	*	$ 2,705	$ 2,705
Office equipment	5 years	107	107
Computers and software	3 years	1,291	1,010
Furniture, fixtures and equipment	5 years	1,249	1,249
		5,352	5,071
Less accumulated depreciation and amortization		(3,155)	(2,258)
Property and equipment, net		$ 2,197	$ 2,813

* Shorter of asset life or lease term.

Depreciation and amortization expense related to property and equipment for the years ended December 31, 2022, 2021 and 2020 was $896, $816, and $690, 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 and derivative liability at December 31, 2022 and 2021 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, 2022 and 2021, 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, 2022 and 2021, 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,		
	2022	2021	2020
Stock options	6,354,544	5,737,599	5,199,235
Restricted stock units	774,166	435,589	176,537
Performance stock units	804,797	956,145	—
Potential common shares	7,933,507	7,129,333	5,375,772

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 $406, $332 and $524 for the years ended December 31, 2022, 2021 and 2020, 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 15.

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.

We have not been required to adopt any accounting standards that had a significant impact on our consolidated financial statements in the three years ended December 31, 2022. We do not expect any recently issued accounting standards to have a significant impact on our consolidated financial statements.

3. Accrued Expenses

Accrued expenses consists of the following:

	December 31, 2022	December 31, 2021
Research and development costs	$ 11,379	$ 17,480
Professional fees	4,502	2,163
Payroll related	11,444	8,371
Royalties	440	791
Inventory	403	26
Sales Allowances	2,710	453
Other	2,016	800
Accrued expenses and other current liabilities	$ 32,894	$ 30,084

4. Fair Value of Financial Assets

The following tables present information about the Company's financial assets and liabilities 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, 2022 using:			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash Equivalents:				
Commercial Paper	$ —	$ 8,484	$ —	$ 8,484
Money Market Funds	99,962	—	—	99,962
Marketable Securities:				
Corporate Debt Securities and Commercial Paper	—	205,611	—	205,611
Total	$ 99,962	$ 214,095	$ —	$ 314,057
Liabilities:				
Derivative liability	$ —	$ —	$ 1,340	$ 1,340
Total	$ —	$ —	$ 1,340	$ 1,340

	Fair value Measurements as of December 31, 2021 using:			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash Equivalents:				
Corporate Debt Securities and 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

As of December 31, 2022 and 2021, the carrying amount of cash and cash equivalents and short-term investments was $333,288 and $294,855, 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 embedded derivative liability associated with our deferred royalty obligation, as discussed further in Note 10, “Long-Term Obligations”, is measured at fair value using an option pricing Monte Carlo simulation model and is included as a component of the deferred royalty obligation. The embedded derivative liability is subject to remeasurement at the end of each reporting period, with changes in fair value recognized as a component of other (expense) income, net. The assumptions used in the option pricing Monte Carlo simulation model include: (1) our estimates of the probability and timing of related events; (2) the probability-weighted net sales of IMCIVREE, including worldwide net product sales, upfront payments, milestones and royalties; (3) our risk-adjusted discount rate that includes a company specific risk premium; (4) our cost of debt; (5) volatility; and (6) the probability of a change in control occurring during the term of the instrument.

The following table sets forth a summary of the changes in the estimated fair value of our embedded derivative liability (in thousands):

	Embedded Derivative
Balance as of December 31, 2021	$ —
Initial recording of embedded derivative	1,590
Change in fair value of derivative	(250)
Balance as of December 31, 2022	$ 1,340

The estimated fair value of the shares of RareStone equity as of our initial recording date and September 30, 2022, as well as the estimated fair value of the derivative liability related to our Royalty Interest Financing Agreement (RIFA) with HealthCare Royalty was determined using Level 3 inputs. The fair value measurement of the RareStone equity as well as the derivative liability are sensitive to changes in the unobservable inputs used to value the financial instrument. Changes in the inputs could result in changes to the fair value of each financial instrument.

The RareStone equity was valued at a de minimis amount and as such written-off during the third quarter of 2022. The Company determined the estimated fair values using a discounted cash flow model under the income approach and an option pricing allocation model. Inherent in discounted cash flow and option pricing allocation models are assumptions related to the equity value of the entity, expected equity volatility, holding period, risk-free interest rate and discount for lack of marketability. The Company estimated equity volatility based on historical volatility of guideline public companies. The risk-free interest rate was based on the U.S. Treasury rates for a maturity similar to the expected holding period.

The following table sets forth a summary of the changes in the estimated fair value of our the RareStone equity (in thousands):

	Year ended December 31,	
	2022	2021
Beginning aggregate estimated fair value of Level 3 securities	$ —	$ —
Initial recording of RareStone equity	1,040	—
Total realized and unrealized losses		
Realized loss included in other expense	(1,040)	—
Ending aggregate estimated fair value of Level 3 securities	$ —	$ —

Marketable Securities

The following tables summarize the Company's marketable securities:

	December 31, 2022			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Assets				
Corporate debt securities and commercial paper (due within 1 year)	$ 205,702	$ —	$ (91)	$ 205,611
	$ 205,702	$ —	$ (91)	$ 205,611

	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

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 2.6 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, 2022, 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.

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, 2022, 2021 and 2020 were $551, $551 and $551, respectively.

Supplemental cash flow information related to the Company's lease for the years ended December 31, 2022, 2021 and 2020, includes cash payments of $818, $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, 2022, all of which is under a non-cancellable operating lease:

	Operating Lease
2023	$ 834
2024	851
2025	502
Thereafter	—
Total operating lease payments	2,187
Less: imputed interest	243
Total operating lease liability	$ 1,944

6. Intangible Assets, Net

As of December 31, 2022, the Company's definite-lived intangible assets, which totaled $7,883, 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, 2022, amortization expense for the next five years and beyond is summarized as follows:

2023	$ 855
2024	855
2025	855
2026	855
2027	855
Thereafter	3,608
Total	$ 7,883

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 $774 and $342 for the years ended December 31, 2022 and 2021, respectively. 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 September 19, 2022, the Company completed a public offering of 4,800,000 shares of common stock at a price to the public of $26.00 per share. The Company received $116,887 in net proceeds after deducting underwriting discounts, commissions and offering expenses. In addition, the Company granted the underwriters a 30-day option to purchase up to an additional 720,000 shares of its common stock at the price to the public, less underwriting discounts and commissions. On October 18, 2022, the Company completed the sale of an additional 580,000 shares of common stock at a price to the public of $26.00 per share pursuant to the partial exercise of the underwriters' option to purchase additional shares, for aggregate net proceeds of approximately $14,175, after deducting underwriting discounts, commissions and offering expenses.

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, 2022, the Company did not sell any shares of common stock under the Sales Agreement. As of December 31, 2022, there was $100.0 million of common stock remaining available for sale under the ATM.

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.

8. Stock-based Compensation

2017 Equity Incentive Plan

The Rhythm Pharmaceuticals, Inc. 2017 Equity Incentive Plan (the “2017 Plan”) provides for the grant of incentive stock options, non-qualified stock options, stock appreciation rights, performance units, restricted stock awards, 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 increases on the first day of each calendar year, 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, 2023, 2022 and 2021, 2,264,497, 2,011,343 and 1,769,436 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 the 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, 2022, an aggregate of 10,149,772 shares of common stock were authorized for issuance under the 2017 Plan, of which a total of approximately 2,726,180 shares of common stock remained available for future awards. In addition, a total of 7,443,592 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.

2022 Inducement Plan

On February 9, 2022, the Company’s board of directors adopted the Rhythm Pharmaceuticals, Inc. 2022 Employment Inducement Plan (the “2022 Inducement Plan”), which became effective on such date without stockholder approval pursuant to Rule 5635(c)(4) of the Nasdaq Stock Market LLC listing rules (“Rule 5635(c)(4)”). The 2022 Inducement Plan provides for the grant of non-qualified stock options, stock appreciation rights, performance units, restricted stock awards, restricted stock units and stock grants. In accordance with Rule 5635(c)(4), awards under the 2022 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 2022 Inducement Plan.

The exercise price of stock options granted under the 2022 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 2022 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 2022 Inducement Plan expire no more than 10 years from the date of grant. As of December 31, 2022, there were 336,780 stock option awards outstanding, 173,135 restricted stock unit awards outstanding and 490,085 shares of common stock available for future grant under the 2022 Inducement Plan.

2017 Employee Stock Purchase Plan

The Company maintains the Rhythm Pharmaceuticals, Inc. 2017 Employee Stock Purchase Plan, (the "2017 ESPP"), which became effective in connection with the completion of the Company's IPO in October 2017. As of December 31, 2022, 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 increases on the first day of each calendar year, 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, 2022, 2021 and 2020, 502,835, 0 and 439,968 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 number of shares available under the 2017 ESPP on January 1, 2023 and 2021. During the year ended December 31, 2022, 38,051 shares were issued under the 2017 ESPP.

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.

Stock Options

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. The Company bases its estimate of expected volatility using a blend of its stock price history for the length of time it has market data for its stock and using 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. 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, 2022, 2021 and 2020, the Company granted 1,929,345, 1,678,230 and 2,546,075 stock option awards pursuant to the 2017 Plan 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 2017 Plan during the years ended December 31, 2022, 2021 and 2020 was $4.14, $15.69 and $13.25, respectively. The total intrinsic value of stock options exercised during the years ended December 31, 2022, 2021 and 2020 was $4,205, $2,688 and $2,661, respectively.

During the years ended December 31, 2022, 2021 and 2020, the Company granted 347,985, 0 and 0 stock option awards pursuant to the 2022 Inducement Plan. 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, 2022, 2021 and 2020 was $13.05, $0 and $0, respectively. The total intrinsic value of stock options exercised was zero during the years ended December 31, 2022, 2021 and 2020.

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,		
	2022	2021	2020
Risk-free interest rate	2.19 %	0.79 %	0.76 %
Expected term (in years)	6.11	6.11	6.08
Expected volatility	69.16 %	69.80 %	70.67 %
Expected dividend yield	—	—	—

A summary of the Company's stock option activity for the year ended December 31, 2022 is as follows:

	Number of Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term	Aggregate Intrinsic Value
Outstanding as of December 31, 2021	5,737,599	$ 21.84	6.73	$ 3,214
Granted	2,277,330	8.50	—	—
Exercised	(697,377)	13.98	—	4,205
Cancelled	(943,008)	22.42	—	—
Outstanding as of December 31, 2022	6,374,544	$ 17.85	7.73	$ 73,994
Options exercisable at December 31, 2022	3,092,723	$ 20.44	6.80	$ 28,317

Restricted Stock Units

The Company may grant restricted stock units ("RSUs") to employees and nonemployee directors under the 2017 Plan and to employees under the 2022 Inducement Plan. 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, 2022 is as follows:

	Number of RSUs	Weighted-Average Grant Date Fair Value
Unvested as of December 31, 2021	435,589	$ 15.74
Granted	597,426	10.48
Vested	(158,546)	20.13
Cancelled	(100,303)	12.78
Unvested as of December 31, 2022	774,166	$ 12.18

As of December 31, 2022, the aggregate intrinsic value of unvested RSUs was $22,544.

Performance Stock Units

In November 2021, the Company granted up to a maximum of 956,145 performance stock units (“PSUs”) to employees under the 2017 Plan. 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 through the vesting date 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, 2022, the Company estimates that 32.3% of the PSUs granted will be eligible to vest.

A summary of the Company's performance stock unit activity for the year ended December 31, 2022 is as follows:

	Number of PSUs	Weighted-Average Grant Date Fair Value
Unvested as of December 31, 2021	956,145	$ 13.24
Granted	—	—
Vested	—	—
Cancelled	(151,348)	13.24
Unvested as of December 31, 2022	804,797	$ 13.24

The following table summarizes the classification of the Company's stock-based compensation expenses related to stock options, restricted stock units, performance stock units and the employee stock purchase plan recognized in the Company's consolidated statements of operations and comprehensive loss.

	Year Ended December 31,		
	2022	2021	2020
Research and development	$ 5,814	$ 7,687	$ 6,055
Selling, general, and administrative	14,017	13,117	11,400
Total	$ 19,831	$ 20,804	$ 17,455

Stock-based compensation expense by award type recognized during the years ended December 31, 2022, 2021 and 2020 was as follows:

	Year Ended December 31,		
	2022	2021	2020
Stock options	$ 15,477	$ 17,988	$ 15,915
Employees stock purchase plan	408	310	180
Restricted stock units	2,918	1,924	1,360
Performance stock units	1,028	582	—
Total	$ 19,831	$ 20,804	$ 17,455

During 2021 and 2020, there were certain awards subject to modification accounting. Per the terms of separation with a former employee, such 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 and $2,880, respectively. During 2022 there was no significant modification of awards.

As of December 31, 2022, the Company has unrecognized compensation cost of $24,752 related to non-vested employee, non-employee and director stock option awards under the 2017 Plan that is expected to be recognized over a weighted-average period of 2.28 years. The Company has unrecognized compensation cost of $7,036 related to non-vested employee restricted stock unit and performance stock unit awards under the 2017 Plan that is expected to be recognized over a weighted-average period of 1.82 years.

As of December 31, 2022, the Company has unrecognized compensation cost of $4,182 related to unvested employee, stock option awards under the 2022 Inducement Plan that is expected to be recognized over a weighted-average period of 3.60 years. As of December 31, 2022, the Company has unrecognized compensation cost of $3,083 related to unvested employee restricted stock unit and stock option awards that is expected to be recognized over a weighted-average period of 3.66 years.

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 POMC, PCSK1 or 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 four independent sub-studies in patients with obesity due to a heterozygous variant of POMC/PCSK1 or LEPR; certain variants of the SRCI gene, and certain variants of the SH2B1 gene. In accordance with the terms of the RareStone License, RareStone made an upfront payment to Rhythm of $7,000 and issued Rhythm 1,077,586 ordinary shares. The Company is eligible to receive development and commercialization milestones of up to $62,500, as well as tiered royalty payments on annual net sales of IMCIVREE.

The Company initially estimated the fair value of the RareStone equity to be $2,440 based on a preliminary valuation during the first quarter of 2022. Upon completion of the valuation procedures during the second quarter of 2022, the Company concluded the initial fair value of the RareStone equity to be $1,040. During the third quarter of 2022, the

Company estimated the fair value of the RareStone equity to be de minimis based upon the results of an updated valuation and recorded an other-than-temporary impairment of $1,040 related to the decline in fair value as a component of other expense in our consolidated statements of operations and other comprehensive loss for the year ended December 31, 2022. The other-than-temporary impairment of $1,040 included the reclassification of a $300 unrealized loss previously recorded as a component of accumulated other comprehensive income (loss) in our condensed consolidated statement of stockholders' equity during the second quarter of 2022.

The Company received total upfront consideration of $8,040 comprised of an upfront payment of $7,000, and the estimated fair value of the RareStone equity of $1,040. The Company determined that the RareStone License contains two performance obligations, the delivery of the license and the supply of clinical and commercial product. The Company further determined the supply of commercial product to RareStone contains a significant future discount and estimates the discount to be $1,286, which is recorded as a component of deferred revenue on the consolidated balance sheet at December 31, 2022.

Based on a relative fair-value allocation between the license and the manufacture of clinical and commercial product, the Company recognized $6,754 of license revenue in the consolidated statements of operations and comprehensive loss during the year ended December 31, 2022. The discount related to commercial manufacturing supply will be deferred and recognized over the commercial supply period or upon termination of the agreement.

On October 28, 2022, the Company delivered a written notice to RareStone that we have terminated the RareStone License for cause. In accordance with the notice, we maintain that RareStone has materially breached its obligations under the RareStone License to fund, perform or seek certain key clinical studies and waivers, including with respect to the Company's global EMANATE trial, among other obligations. On December 21, 2022, RareStone provided written notice to the Company that it objects to the claims in our October 28, 2022 notice, including the Company's termination of the RareStone License for cause. RareStone may attempt to cure the alleged breaches, which the Company believe to be incurable, within the timeframe specified under the RareStone License.

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 and $4,000 commercial milestone as a finite-lived intangible asset, as a result of the first commercial sale of IMCIVREE in the U.S. and Europe during March 2021 and March 2022, respectively. The Company recorded development 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 2022 or 2021.

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. The Company recorded development milestone expenses related to this license agreement of $1,000 during the year ended December 31, 2022. The expenses were recorded as research and development expenses when the milestone criteria were met in full during 2022. There are no research and development expenses related to milestones recorded in 2021 or 2020.

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.* There were no milestone expenses related to this license for the years ended December 31, 2022, 2021 and 2020, respectively. We have notified Takeda that the Company has halted development activities related to RM-853.

10. Long-Term Obligations

On June 16, 2022, we entered into a RIFA with entities managed by HealthCare Royalty Management, LLC, collectively referred to as the Investors. Pursuant to the RIFA and subject to customary closing conditions, the Investors have agreed to pay the Company an aggregate investment amount of up to $100,000, or the Investment Amount. Under the terms of the RIFA, we received $37,500 on June 29, 2022 upon FDA approval of IMCIVREE in BBS, referred to as the Initial Investment Amount, and we received an additional $37,500 on September 29, 2022 of the Investment Amount upon EMA approval for BBS. We are entitled to receive the remaining $25,000 of the Investment Amount forty-five business days following achievement of a specified amount of cumulative net sales of IMCIVREE between July 1, 2022 and September 30, 2023.

As consideration for the Investment Amount and pursuant to the RIFA, we agreed to pay the Investors a tiered royalty on our annual net revenues, or Revenue Interest, including worldwide net product sales and upfront payments and milestones. The applicable tiered percentage will initially be 11.5% on annual net revenues up to $125,000, 7.5% on annual net revenues of between $125,000 and $300,000 and 2.5% on annual net revenues exceeding $300,000. If the Investors have not received cumulative minimum payments equal to 60% of the amount funded by the Investors to date by March 31, 2027, or 120% of the amount funded by the Investors to date by March 31, 2029, we must make a cash payment immediately following each applicable date to the Investors sufficient to gross the Investors up to such minimum amounts after giving full consideration of the cumulative amounts paid by us to the Investors through each date, referred to as the Under Performance Payment. As the repayment of the funded amount is contingent upon worldwide net product sales and upfront payments, milestones, and royalties, the repayment term may be shortened or extended depending on actual worldwide net product sales and upfront payments, milestones, and royalties. As of December 31, 2022 we have made $132 of payments.

The Investors' rights to receive the Revenue Interests will terminate on the date on which the Investors have received payments equal to a certain percentage of the funded portion of the Investment Amount including the aggregate

of all payments made to the Investors as of such date, each percentage tier referred to as the Hard Cap, unless the RIFA is earlier terminated. The total Revenue Interests payable by us to the Investors is capped between 185% and 250% of the Investment Amount paid, dependent on the aggregate royalty paid between 2028 and 2032. If a change of control of occurs, the Investors may accelerate payments due under the RIFA up to the Hard Cap plus any other obligations payable under the RIFA.

The repayment period commenced on July 8, 2022 for the Initial Investment Amount, and expires on the earlier of (i) the date at which the Investors received cash payments totaling an aggregate of a Hard Cap ranging from 185% to 250% of the Initial Investment Amount or (ii) the legal maturity date of July 8, 2034. If the Investors have not received payments equal to 250% of the Investment Amount by the twelve-year anniversary of the initial closing date, we will be required to pay an amount equal to the Investment Amount plus a specific annual rate of return less payments previously received by Investors. In the event of a change of control, we are obligated to pay Investors an amount equal to the Hard Cap in effect at the time, ranging from 185% to 250% plus any Under Performance Payment of the Investment Amount less payments previously received by Investors. In addition, upon the occurrence of an event of default, including, among others, our failure to pay any amounts due to Investors under the deferred royalty obligation, insolvency, our failure to pay indebtedness when due, the revocation of regulatory approval of IMCIVREE in the U.S. or our breach of any covenant contained in the RIFA and our failure to cure the breach within the prescribed time frame, we are obligated to pay Investors an amount equal to the Hard Cap in effect at the time of default ranging from 185% to 250% plus any Under Performance Payment of the Investment Amount less payments previously received by Investors. In addition, upon an event of default, Investors may exercise all other rights and remedies available under the RIFA, including foreclosing on the collateral that was pledged to Investors, which consists of all of our present and future assets relating to IMCIVREE.

We have evaluated the terms of the RIFA and concluded that the features are similar to those of a debt instrument. Accordingly, we have accounted for the transaction as long-term debt and presented it as a deferred royalty obligation on our consolidated balance sheets. We have further evaluated the terms of the RIFA and determined that the repayment of the Hard Cap in effect at the time which ranges from 185% to 250% of the Investment Amount, less any payments made to date, upon a change of control is an embedded derivative that requires bifurcation from the debt instrument and fair value recognition. We determined the fair value of the derivative using an option pricing Monte Carlo simulation model taking into account the probability of change of control occurring and potential repayment amounts and timing of such payments that would result under various scenarios, as further described in Note 4, “Fair Value of Financial Instruments” to our consolidated financial statements. During the second quarter of 2022, the Company recorded $1,590 for the initial fair value of the embedded derivative liability. The fair value of the embedded derivative liability was $1,340 as of December 31, 2022. We will remeasure the embedded derivative to fair value each reporting period until the time the features lapse and/or termination of the deferred royalty obligation. For the year ended December 31, 2022 we recognized other income in the amount of $250, due to the remeasurement of the embedded derivative liability. The carrying value of the deferred royalty obligation at December 31, 2022 was $75,810 based on $75,000 of proceeds, net of the initial fair value of the bifurcated embedded derivative liability upon execution of the RIFA, and debt issuance costs incurred. The carrying value of the deferred royalty obligation approximated fair value at December 31, 2022. The effective interest rate as of December 31, 2022 was 16.22%. In connection with the deferred royalty obligation, we incurred debt issuance costs totaling $2,662. Debt issuance costs have been netted against the debt and are being amortized over the estimated term of the debt using the effective interest method, adjusted on a prospective basis for changes in the underlying assumptions and inputs. The assumptions used in determining the expected repayment term of the debt and amortization period of the issuance costs requires that we make estimates that could impact the classification of these costs, as well as the period over which these costs will be amortized.

11. 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, 2022, the Company does not expect to make milestone payments due to third parties during the next 12 months from the filing of this Annual Report on Form 10-K, 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.

12. Related-Party Transactions

Amounts paid directly to consultants and vendors considered to be related parties amounted to $1,868, $1,961 and $3,221, for the years ended December 31, 2022, 2021 and 2020, respectively. Outstanding payments due to these related parties as of December 31, 2022 and 2021 were $13 and $50, respectively, and were included within accounts payable on the consolidated balance sheets.

13. Income Tax

For the years ended December 31, 2022, 2021 and 2020 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,		
	2022	2021	2020
Statutory tax rate	21.00 %	21.00 %	21.00 %
State tax, net of federal benefit	9.83 %	7.45 %	6.32 %
Research and development credit	0.78 %	2.94 %	1.46 %
Orphan drug credit	2.15 %	7.58 %	2.40 %
Tax law change	— %	— %	— %
Stock compensation	(0.29)%	(1.05)%	(0.53)%
Other	(0.04)%	(0.47)%	(0.30)%
Change in valuation allowance	(33.44)%	(37.45)%	(30.35)%
Effective tax rate	— %	— %	— %

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

	As of December 31,	
	2022	2021
Deferred tax assets:		
Net operating loss carryforwards	$ 135,470	$ 113,098
Research and development credits	14,380	13,477
Orphan drug credit	19,281	15,385
Capitalized license fee	2,776	2,651
Stock-based compensation	11,074	9,150
Capitalized research and development costs	29,663	—
Deferred revenue	438	1,901
Accrued expenses & other	4,536	2,976
Total deferred tax assets	217,618	158,638
Valuation allowance	(217,257)	(158,211)
Net deferred tax assets	361	427
Deferred tax liabilities:		
Operating lease right-of-use asset and other	(361)	(427)
Total deferred tax liabilities	$ (361)	$ (427)

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, 2022 and 2021, 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 $59,046 in 2022 and $24,615 in 2021 primarily relates to the net loss incurred by the Company during each period.

As of December 31, 2022, the Company had federal and state net operating loss carryforwards of approximately $494,500 and $484,606, 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, 2022, $421,334 can be carried forward indefinitely.

As of December 31, 2022, the Company had federal and state research tax credits of approximately $11,575 and $3,550, respectively, which may be used to offset future tax liabilities. Additionally, as of 2022, the Company had a federal orphan drug credit related to qualifying research of $19,281. 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, 2022 and 2021. 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.

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, 2022 and 2021, 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.

14. 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, 2022, 2021 and 2020 were $1,195, $886 and $321 , respectively.

15. 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 within the above notes to these consolidated financial statements, and except as described below.

Business Combination

On February 27, 2023, the Company, through its wholly-owned Dutch subsidiary, Rhythm Pharmaceuticals Netherlands B.V., a Dutch private limited liability company (“Rhythm BV”), entered into a Share Purchase Agreement (the “Purchase Agreement”) with Xinvento B.V., a Dutch private limited liability company based in the Netherlands (“Xinvento”), and the other parties named therein, pursuant to which, and concurrently with the execution thereof, Rhythm BV acquired all of the issued and outstanding shares of Xinvento for aggregate consideration at closing of $5,000, as adjusted pursuant to the terms of the Purchase Agreement and subject to the distribution and payment terms set forth therein (the “Closing Purchase Price”).

In addition to the Closing Purchase Price, the Purchase Agreement provides for the payment of additional consideration totaling up to $206.0 million upon achievement of certain development, regulatory and commercial milestones by Xinvento, as follows: (i) up to an aggregate of $6.0 million in clinical development milestones; (ii) up to an aggregate of $125,000 in regulatory approval and commercial milestones; and (iii) up to an aggregate of $75,000 in sales milestones in the event a second molecule is selected, developed and approved.

Upon completion of the acquisition, Xinvento became a wholly owned subsidiary of Rhythm BV.

The Purchase Agreement contains customary representations, warranties and covenants, including covenants by Sellers (as defined in the Purchase Agreement) to indemnify Rhythm BV and certain related parties for breaches of certain representations, warranties and covenants in the Purchase Agreement, subject to customary exclusions and caps.

The business combination is intended to expand our pipeline into congenital hyperinsulinism (CHI), a rare disease that is well aligned with our corporate strategy and our focus on rare endocrinology indications. During the year ended December 31, 2022, the Company incurred total acquisition-related costs of $62 related to the transaction. As the transaction occurred subsequent to period-end, the Company is still evaluating the purchase price allocation of the transaction but expects the primary assets acquired to be intangible assets and goodwill. Acquired tangible assets and assumed liabilities are expected to be immaterial. The allocation is expected to be finalized during the first half of 2023.

Exhibit 2.2

Execution Version

SHARE PURCHASE AGREEMENT

BY AND AMONG

RHYTHM PHARMACEUTICALS NETHERLANDS B.V.,

THE SELLERS LISTED ON THE SIGNATURE PAGE HERETO,

XINVENTO B.V.

AND

THE SELLER REPRESENTATIVE IDENTIFIED HEREIN

DATED AS OF FEBRUARY 24, 2023

CONTENTS

EXHIBITS AND SCHEDULES

SHARE PURCHASE AGREEMENT

THIS SHARE PURCHASE AGREEMENT (this "Agreement") is made as of February 24, 2023 (the "Agreement Date"), by and among (a) Rhythm Pharmaceuticals Netherlands B.V., a Dutch private limited liability company (*besloten vennootschap met beperkte aansprakelijkheid*) having its corporate seat in Amsterdam, the Netherlands, and its address at Radarweg 29, 1043 NX Amsterdam, the Netherlands, registered with the trade register of the Dutch Chamber of Commerce under number 83439315 ("Buyer"), (b) Xinvento B.V., a Dutch private limited liability company (*besloten vennootschap met beperkte aansprakelijkheid*) having its corporate seat in Amsterdam, the Netherlands, and its address at Brouwersgracht 187 H, 1015 GJ Amsterdam, the Netherlands and registered with the trade register of the Dutch Chamber of Commerce under number 83632581 (the "Company"), (c) the existing shareholders of the Company listed on Schedule A hereto (each individually "Seller", and collectively, "Sellers"), and (d) Thudaumot Holding, B.V., a Dutch private limited liability company (*besloten vennootschap met beperkte aansprakelijkheid*), in its capacity as Seller Representative (as defined in Section 9 hereto).

WHEREAS, Sellers constitute all of the shareholders of the Company, and Sellers are the record and beneficial owners of all of the issued and outstanding shares of the Company (collectively, the "Shares") as set forth in Schedule A.

WHEREAS, on the terms and subject to the conditions set forth in this Agreement, Buyer desires to purchase from Sellers, and Sellers desire to sell to Buyer, all of the Shares held by Sellers for the consideration described herein (the "Acquisition").

NOW, THEREFORE, in consideration of the mutual representations, warranties, covenants and agreements set forth in this Agreement (defined terms having the meanings indicated in Section 1.1 or otherwise as defined elsewhere in this Agreement), and for other good and valuable consideration, the receipt of which is hereby acknowledged, Buyer, Sellers, the Company and Seller Representative, intending to be legally bound, agree as follows:

Section 1.
DEFINITIONS AND INTERPRETATIONS

1.1 Certain Definitions. For purposes of this Agreement, the following terms shall have the following meanings:

"Accounting Arbitrator" has the meaning set forth in Section 2.5(f).

"Accounting Expert" has the meaning set forth in Section 2.9(g)(ii).

"Acquisition" has the meaning set forth in the Preamble.

"Action" means any action, suit, litigation, arbitration, investigation or other proceeding, whether civil or criminal, in law or in equity, in each case, by or before any Governmental Authority or arbitrator.

"Adjusted Purchase Price" has the meaning set forth in Section 2.5(a).

"Adjustment Time" means 12:01 a.m. eastern time on the Closing Date.

"Advance Amount" has the meaning set forth in Section 9.1(f).

"Affiliate" means, with respect to any Person, any other Person that, directly or indirectly through one (1) or more intermediaries, controls, is controlled by or is under common control with such Person, and the term "control" (including the terms "controlled by" and "under common control with") means the possession, directly or indirectly, of the power to direct or cause the direction of the management and policies of such Person, whether through ownership of voting securities, by contract or otherwise.

"Aggregate Purchase Price" means the sum of (i) the Purchase Price, (ii) plus the Closing Cash (as conclusively determined in accordance with Section 2.5(e)(iii)), and (iii) plus the Milestone Payments, if any, that have been finally determined to be achieved.

"Agreement" has the meaning set forth in the Preamble.

"Agreement Date" has the meaning set forth in the Preamble.

"Ancillary Agreements" means each of the other written agreements, documents, statements, certificates and instruments to be delivered by Sellers or the Company pursuant to Section 2.7 or by Buyer pursuant to Section 2.8.

"Audit" means any audit, assessment, claim, examination, visit or other inquiry relating to Taxes by any Tax Authority or any judicial or administrative proceeding relating to Taxes.

"Benefit Plan" means any material plan, agreement, policy, or arrangement providing bonuses or other incentive compensation, severance, retention, change in control, deferred compensation, or equity compensation, in each case, maintained by the Company in which any current or former employee, director, manager or consultant of the Company, or any beneficiary thereof, has a present or future right to benefits and under which the Company has any Liability.

"Business Day" means any day of the year on which national banking institutions in the Commonwealth of Massachusetts and Amsterdam, the Netherlands are open to the public for conducting business and are not required or authorized by law to close.

"Buyer" has the meaning set forth in the Preamble.

"Buyer Indemnified Parties" has the meaning set forth in Section 7.4.

"Cash" means the aggregate amount of all cash and cash equivalents of the Company required to be reflected as cash and cash equivalents on a consolidated balance sheet of the Company prepared in accordance with GAAP, using the policies, conventions, methodologies and procedures used in preparing the Financial Statements, net of (i) any outstanding checks, wires and bank overdrafts of the Company or its Subsidiaries; (ii) any amounts relating to credit card receivables or Restricted Cash; and (iii) any security deposits and other deposits or transfers received or deposited for the account of the Company or its Subsidiaries, in the case of each of clauses (i), (ii) and (iii), whether or not required to be reported as such under GAAP.

"CHI" means congenital hyperinsulinism.

"Closing" has the meaning set forth in Section 2.6(a).

"Closing Balance Sheet" has the meaning set forth in Section 2.5(e)(i).

"Closing Cash" means the aggregate amount of Cash held by the Company, as of the Adjustment Time.

"Closing Date" has the meaning set forth in Section 2.6(a).

"Closing Date Schedule" has the meaning set forth in Section 2.5(e)(i).

"Closing Deliverables" means the closing deliverables of Sellers provided for in Section 2.7 and the closing deliverables provided for in Section 2.8.

"Code" means the United States Internal Revenue Code of 1986, as amended.

"Company" has the meaning set forth in the Preamble.

"Company Debt" means the aggregate amount of all Indebtedness of the Company outstanding as of immediately prior to the Closing. For the avoidance of doubt, "Company Debt" shall include the aggregate Convertible Loan Repayment Amounts.

"Company Governing Documents" means the Company's (a) articles of incorporation, articles of association or other applicable similar organizational or charter documents relating to the creation or organization of the Company, and (b) shareholders' agreement, or other applicable similar documents relating to the operation, governance or management of the Company.

"Company Know-How" means the Company's proprietary and confidential information, techniques, methods, processes, data, results, inventions, discoveries, designs, formulas, compositions, applications, and improvements that the Company (or a third party for and on behalf of the Company) has developed, acquired or used prior to the Closing Date or develops, acquires, or uses on the Closing Date and thereafter in connection with the identification, synthesis, characterization, optimization, modification, testing, evaluation, production, or use of molecules that behave as a K_{ATP} channel opener or target SUR1/Kir6.2 for various purposes, such as drug discovery, diagnostics, biotechnology, materials science, or nanotechnology. The Company Know-How relating to molecules that behave as a K_{ATP} channel opener or target SUR1/Kir6.2 includes, but is not limited to, the following:

(i) The molecular structures, properties, functions, interactions, and mechanisms of action of the molecules that behave as a K_{ATP} channel opener or target SUR1/Kir6.2 and their analogs, derivatives, variants, precursors, intermediates, metabolites, conjugates, complexes, or combinations;

(ii) The synthetic routes, protocols, conditions, reagents, catalysts, solvents, equipment, and analytical methods used to prepare, purify, isolate, identify, quantify, or characterize the molecules that behave as a K_{ATP} channel opener or

target SUR1/Kir6.2 and their analogs, derivatives, variants, precursors, intermediates, metabolites, conjugates, complexes, or combinations;

(iii) The assays, models, systems, platforms, tools, software, databases, algorithms, or parameters used to screen, evaluate, optimize, modify, or test the molecules that behave as a K_{ATP} channel opener or target SUR1/Kir6.2 and their analogs, derivatives, variants, precursors, intermediates, metabolites, conjugates, complexes, or combinations for their biological, chemical, physical, or pharmacological activity, efficacy, safety, stability, solubility, bioavailability, biodistribution, pharmacokinetics, pharmacodynamics, toxicity, or potential therapeutic or diagnostic applications;

(iv) The publications, reports, presentations, or other documents or records that disclose, describe, or document any aspect of the items listed under (i) through (iii) above relating to molecules that behave as a K_{ATP} channel opener or target SUR1/Kir6.2 or that are derived from or based on the items listed under (i) through (iii) above relating to molecules that behave as a K_{ATP} channel opener or target SUR1/Kir6.2; and

(v) The trade secrets, confidential information, or other intellectual property rights that protect or cover any aspect of the items listed under (i) through (iii) above relating to molecules that behave as a K_{ATP} channel opener or target SUR1/Kir6.2 or that are derived from or based on the items listed under (i) through (iii) above relating to molecules that behave as a K_{ATP} channel opener or target SUR1/Kir6.2.

"Confidentiality Agreement" has the meaning set forth in Section 6.1.

"Consents" has the meaning set forth in Section 3.6.

"Contract" means any legally binding agreement, contract, subcontract, settlement agreement, lease, instrument, note, option, warranty, license, sublicense, insurance policy or legally binding commitment, arrangement, obligation or undertaking of any nature, including all amendments to any of the foregoing.

"Convertible Loan Agreements" means the convertible loan agreements between the Company and the Persons set forth in Schedule 2.7(m).

"Convertible Loan Holders" the Persons set forth in Schedule 2.7(m).

"Convertible Loan Repayment Amount" means, with respect to any Convertible Loan, the principal amount of such Convertible Loan plus accrued and unpaid interest thereon up to the Closing Date, multiplied by approximately 2.1 (two and one tenth).

"Convertible Loan" means a convertible loan extended to the Company by the Convertible Loan Holders pursuant to the Convertible Loan Agreements.

"Deed of Transfer" has the meaning set forth in Section 2.2.

"Determination Period" has the meaning set forth in Section 2.9(g)(i).

"Disclosure Schedule" has the meaning set forth in Section 3.

"Dispute Period" has the meaning set forth in Section 7.7(b).

"Distribution Methodology" means the Distribution Methodology described in Schedule 2.5(c)(vi) attached hereto.

"Environmental Laws" means all Legal Requirements in effect as of the date hereof relating to pollution or protection of the environment, including those relating to the Release or threatened Release of Hazardous Materials to the environment.

"Estimated Closing Cash" has the meaning set forth in Section 2.5(c)(iii).

"Estimated Company Debt" has the meaning set forth in Section 2.5(c)(ii).

"Estimated Seller Transaction Expenses" has the meaning set forth in Section 2.5(c)(iv).

"FDA" means the United States Food and Drug Administration.

"FDCA" means the Federal Food, Drug, and Cosmetic Act.

"Final Determination" has the meaning set forth in Section 7.11.

"Financial Statements" has the meaning set forth in Section 3.8(a).

"Fundamental Representations" has the meaning set forth in Section 7.2.

"GAAP" means Dutch generally accepted accounting principles, consistently applied and maintained throughout the periods indicated.

"Governmental Authority" means any national, federal, state, municipal, local or foreign government, or political subdivision thereof, any supranational organization (e.g., the European Union), any authority, agency, commission, department, bureau or other instrumentality entitled to exercise any administrative, executive, judicial, legislative, policy, regulatory, legal or Taxing power, any court or tribunal (or any department, bureau or division thereof), any arbitrator or arbitration panel, or any other self-regulatory or quasi-governmental authority of any nature.

"Hazardous Material" means any material, chemical, substance, pollutant, contaminant, waste, waste waters, or byproducts defined as or included in the definition of "hazardous substances," "hazardous wastes," "hazardous materials," "toxic pollutants," "contaminants," "pollutants," "toxic substances," or words of similar import under any Environmental Law, including oil, petroleum, petroleum product, or petroleum based or derived substance or waste, asbestos containing materials, polychlorinated biphenyls, and per- and polyfluoroalkyl substances.

"Health Care Laws" means (a) the FDCA; (b) federal and state fraud and abuse laws, including, the federal Anti-Kickback Statute (42 U.S.C. § 1320a-7b(b)), the civil False Claims Act (31 U.S.C. §3729 et seq.), §§ 1320a-7 and 1320a-7a of Title 42 of the United States Code, the

criminal false statements law (42 U.S.C. Section 1320a-7b(a)), 18 U.S.C. §§ 286, 287, 1035, 1347, 1349 and the health care fraud criminal provisions under the U.S. Health Insurance Portability and Accountability Act of 1996 ("HIPAA") (42 U.S.C. § 1320d et seq.) and the Physician Payments Sunshine Act (42 U.S.C. § 1320-7h); (c) HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act (42 U.S.C. § 17921 et seq.) and the regulations promulgated thereunder; (d) Titles XVII (42 U.S.C. §1395 et seq.) and XIX (42 U.S.C. §1396 et seq.) of the Social Security Act, and any applicable Legal Requirements governing government funded or sponsored healthcare programs; and (e) the regulations promulgated thereunder and all other statutes, directives, rules or regulations applicable to the ownership, testing, development, manufacture, quality, safety, accreditation, packaging, use, distribution, labeling, promotion, sale, offer for sale, import, export or disposal of any product or product candidate manufactured, developed, tested, imported, exported, advertised, promoted, sold or distributed by the Company.

"Holdback Amount" means $500,000.

"Holdback Period" has the meaning set forth in Section 7.10(b).

"Indebtedness" means, without duplication, (a) all obligations for borrowed money (including such amounts that would become due as a result of the consummation of the transactions contemplated by this Agreement); (b) all obligations evidenced by notes, bonds, debentures, mortgage or other instruments; (c) all obligations under any debt security, interest rate, currency or other hedging or swap, derivative obligation or other similar arrangement; (d) Pandemic-Relief Debt; (e) all reimbursement obligations under letters of credit (only to the extent drawn or funded) or similar facilities; (f) all contingent amounts owing with respect to prior purchases of businesses or companies; (g) all guarantees, including guarantees of any items set forth in clauses (a) through (f); (h) any amounts for the deferred purchase price of goods and services, including any earn out liabilities associated with past acquisitions; (i) all liabilities with respect to any current or former employee or director of the Company or any of its Subsidiaries that arise before or on the Closing Date, including all liabilities with respect to any Benefit Plan, all accrued salary, deferred compensation and vacation obligation, all workers' compensation claims, any liabilities in respect of accrued but unpaid bonuses for the prior fiscal year and for the period commencing on the first day of the fiscal year and ending on the Closing Date, and any employment Taxes payable by the Company or any of its Subsidiaries with respect to the foregoing; (j) all unpaid Taxes for any Pre-Closing Tax Period, including any income Tax liabilities or deferred payroll Taxes (*loonheffing*) relating to events occurring or periods or portions thereof ending on or prior to the Closing Date; (k) unpaid management fees; (l) all deposits and monies received in advance; (m) all outstanding prepayment premiums, if any; and accrued interest, fees and expenses related to any of the items set forth in clauses (a) through (m); and (n) all obligations of the type referred to in clauses (a) through (m) of other Persons for the payment of which the Company is responsible or liable, as obligor, guarantor, surety or otherwise, including any guarantee of such obligations. For the avoidance of doubt, "Indebtedness" shall exclude Seller Transaction Expenses.

"Indemnified Party" has the meaning set forth in Section 7.7(a).

"Indemnifying Party" has the meaning set forth in Section 7.7(a).

"Independent Member" has the meaning set forth in Section 6.5(b).

"Initial Closing Statement" has the meaning set forth in Section 2.5(c).

"Intellectual Property" means all intellectual property rights of any type in any jurisdiction throughout the world, whether registered or unregistered, whether published or not published, including the following: (a) all inventions, patents, patent applications, and patent disclosures, together with all reissuances, continuations, continuations-in-part, revisions, divisions, extensions, and reexaminations thereof, (b) all registered and unregistered trademarks, service marks, trade dress, and logos, and all applications, registrations, and renewals in connection therewith, (c) all copyrightable works, all copyrights and all registrations and renewals in connection therewith, (d) all trade secrets and other confidential business information, (e) all domain names, social media identifiers, URLs, and registrations in respect thereof, (f) all rights to claim priority to, file an applicable for, and obtain a grant, renewal and extension in connection with any of the foregoing, (g) all applications, registrations and renewals in connection with any of the foregoing and (h) all copies and tangible embodiments of any of the foregoing.

"Intellectual Property License" means any license, sublicense, right, covenant, non-assertion, permission, consent, release or waiver under or with respect to any Intellectual Property.

"Interim Balance Sheet" has the meaning set forth in Section 3.8(a).

"Interim Financial Statements" has the meaning set forth in Section 3.8(a).

"IRS" means the United States Internal Revenue Service.

"Joint Steering Committee" has the meaning set forth in Section 6.5(a).

"JSC Member" has the meaning set forth in Section 6.5(a).

"Knowledge" (a) of the Sellers, with respect to any fact or matter in question, means the actual knowledge of Claudine van der Sande, Piet Wigerinck, Sarah Hafith-de Boer, without any duty to investigate or conduct independent inquiry, and (b) of the Buyer, with respect to any fact or matter in question, means all facts that are actually known by such party without any duty to investigate or conduct independent inquiry.

"Lead Candidate" has the meaning set forth in Section 2.9(k)(i).

"Legal Requirements" means any and all applicable federal, state, local, municipal, provincial, territorial, national, foreign or other law, statute, constitution, directive, resolution, ordinance, code, edict, decree, order (including executive orders), rule, judgment, injunction, writ, regulation or ruling enacted, adopted, promulgated, implemented or otherwise put into effect by or under the authority of any Governmental Authority.

"Liabilities" means with respect to any Person, any liability of such Person of any kind, whether absolute or contingent, known or unknown, accrued or unaccrued, asserted or unasserted, matured or un-matured, fixed, disputed, liquidated or executory, in each case to the extent required to be recorded or reflected on a balance sheet prepared in accordance with GAAP.

"Liens" means any mortgage, license, charge, interest, pledge, claim, lien, encumbrance, option, security interest, restriction on the right to sell, transfer or dispose (and in the case of securities, vote) or other adverse claim of any kind or nature whatsoever (whether arising by contract or by operation of law and whether voluntary or involuntary).

"Loss" or "Losses" means the damages (*vermogensschade*) suffered by the Buyer, whereby the loss of the Company shall be attributed to the Buyer, a party as set forth in Title 1, Section 10 of Book 6 of the Dutch Civil Code, including any liabilities in respect of Tax, including any fines, penalties, interest or additional amount in respect of Tax or otherwise in connection therewith.

"Material Adverse Effect" means any change or effect that is materially adverse (A) to the business, operations, financial condition or results of operations of the Company; provided, however, that none of the following shall be deemed, either alone or in combination with any other change, event, occurrence, state of facts, development or effect, to constitute, and no change, event, occurrence, state of facts, development or effect arising from or attributable or relating to any of the following shall be taken into account in determining whether there has been, a Material Adverse Effect: (i) conditions affecting the industries in which the Company operates or participates, the political conditions of the U.S. or any foreign country in any location where the Company operates, the U.S. economy or financial markets or any foreign markets or any foreign economy or financial markets in any location where the Company operates, including changes in interests rates, which do not affect the Company disproportionately from other participants in the industries or markets in which the Company operates or participates; (ii) compliance by the Company with the terms of, or the taking of any action by the Company required by, this Agreement, or otherwise taken with the consent of Buyer; (iii) any change in GAAP or in accounting standards, or applicable laws (or interpretation thereof); (iv) any acts of God, epidemics or pandemics (including COVID-19), calamities, acts of war, terrorism or military action or the escalation thereof, national or international political, general economic, social conditions or changes in the financial or capital markets (or any escalation or worsening of any of the foregoing); (v) any action required to be taken under applicable laws, including any actions taken or required to be taken by the Company in order to obtain any approval or authorization for the consummation of the transactions contemplated hereby under applicable antitrust or competition laws; (vi) any failure, in and of itself, by the Company to meet any projections, forecasts, or revenue or earnings predictions for any period (it being understood that the facts and circumstances giving rise or contributing to such failure may be taken into account in determining whether there has been a Material Adverse Effect); provided that, with respect to clauses (i), (iii), (iv) and (vi), the impact of such change, event, occurrence, state of facts, development or effect is not disproportionate to the Company, taken as a whole, as compared to other similarly situated companies; or (B) to the ability of the Company to perform its material obligations under this Agreement or to consummate the transactions contemplated hereby on a timely basis.

"Material Contract" has the meaning set forth in Section 3.13(a).

"Material Suppliers" has the meaning set forth in Section 3.14.

"Milestone" has the meaning set forth in Section 2.9(a).

"Milestone Achievement Notice" has the meaning set forth in Section 2.9(a).

"Milestone Payment" has the meaning set forth in Section 2.9(a).

"Net Sales" has the meaning set forth in Section 2.9(k)(i).

"Net Sales Achievement Notice" has the meaning set forth in Section 2.9(g)(ii).

"Net Sales Dispute Notice" has the meaning set forth in Section 2.9(g)(ii).

"Net Sales Milestone" has the meaning set forth in Section 2.9(c).

"Notary" means any civil law notary of NautaDutilh, located at Beethovenstraat 400, (1082 PR) Amsterdam, the Netherlands.

"Notice" has the meaning set forth in Section 7.7(a).

"Pandemic-Relief Debt" means any Indebtedness incurred in connection with any Legal Requirement or program involving any Governmental Authority providing or expanding any loan, guaranty, investment, participation, grant, program or other assistance in response to or to provide relief for the COVID-19 pandemic. "Pension Arrangement" has the meaning set forth in Section 3.18(g).

"Permits" means all permits, approvals, concessions, grants, franchises, licenses, registrations, clearances, certificates, declarations of conformity, rights, qualifications, privileges, exemptions, authorizations, easements, variances, permissions, identification numbers, consents or orders of, or filings with, notifications to or lodged with, any Governmental Authority or any other Person, together with all applications therefor and all renewals, extensions, or modifications thereof and additions thereto.

"Permitted Liens" means (a) Liens for Taxes not yet due and payable or being contested in good faith by appropriate proceedings for which adequate reserves have been established, (b) statutory Liens of landlords, (c) Liens of carriers, warehousemen, mechanics, materialmen and repairmen incurred in the ordinary course of business and not yet delinquent or due or payable, or are being contested in good faith through appropriate proceedings, (d) immaterial Liens that do not adversely affect the use or value of the asset(s) subject thereto, (e) with respect to real property, Liens and easements due to zoning and subdivision laws and regulations, (f) with respect to real property, reservations, restrictions, easements, limitations, conditions and other Liens of public record and (g) Liens that will be terminated or released at the Closing in connection with the repayment of Company Debt at the Closing.

"Permitted Transfer" has the meaning set forth in Section 2.9(h).

"Person" means any individual, corporation, partnership, limited liability company, firm, joint venture, association, joint-stock company, trust, unincorporated organization, Governmental Authority or other entity.

"Personal Information" has the meaning set forth in Section 3.17.

"Post-Closing Payment Set-Off" has the meaning set forth in Section 7.11.

"Pre-Closing Tax Period" means any Taxable period ending on or before the Closing Date and that portion of any Straddle Period ending on the Closing Date.

"Privacy Laws" has the meaning set forth in Section 3.17.

"Pro Rata Portion" shall mean the percentage of the total number of Shares held by each Seller prior to the Closing divided by the total number of outstanding Shares prior to the Closing and as set forth on Schedule A hereto. For the avoidance of doubt, the sum of all Pro Rata Portions of the Sellers shall be one hundred percent (100%).

"Product" has the meaning set forth in Section 2.9(k)(iii).

"Project Return Agreement" means the agreement to be entered into by the Buyer and the Project Return Entity upon the occurrence of one of the scenarios described in Section 6.5(c), which agreement sets out the terms and conditions of the license of all applicable data, information, materials, and intellectual property rights generated by or for Buyer to the Project Return Entity as set forth in Section 6.5(c), which will stipulate (i) protective provisions for the benefit of the Project Return Entity customary for a license agreement and (ii) the Buyer's obligation to prosecute, maintain and enforce the object of the license consistent with optimizing patent strategy.

"Project Return Entity" means a special purpose vehicle that will be incorporated by, or on behalf of, and controlled by Claudine van der Sande as a Dutch private limited liability company (*besloten vennootschap met beperkte aansprakelijkheid*) upon the occurrence of one of the scenarios described in Section 6.5(c), which special purpose vehicle will enter into and be the beneficiary of the Project Return Agreement.

"Purchase Price" means $5,000,000.

"Purchase Price Deficiency" has the meaning set forth in Section 2.5(g).

"Purchase Price Surplus" has the meaning set forth in Section 2.5(g).

"Registered Company Intellectual Property" has the meaning set forth in Section 3.16(a).

"Registered Company Patents" has the meaning set forth in Section 3.16(a).

"Regulatory Authorities" has the meaning set forth in Section 3.22(a).

"Regulatory Expert" has the meaning set forth in Section 2.9(g)(i).

"Regulatory Milestone" has the meaning set forth in Section 2.9(c).

"Regulatory Milestone Achievement Notice" has the meaning set forth in Section 2.9(g)(i).

"Regulatory Milestone Dispute Notice" has the meaning set forth in Section 2.9(g)(i).

"Regulatory Permits" has the meaning set forth in Section 3.22(b).

"Related Party" means any present director or shareholder of the Company or any Affiliate of the Company.

"Release" means any releasing, spilling, leaking, pumping, pouring, emitting, emptying, discharging, injecting, escaping, leaching, dumping, or disposing.

"Releasee" has the meaning set forth in Section 6.4(a).

"Representatives" means with respect to any Person its respective directors, members of its board of managers, officers, employees, agents, advisors, affiliates and representatives (including attorneys, accountants, consultants, bankers and financial advisors).

"Restricted Cash" means all Cash and Cash equivalents that are not freely useable and available to the Company or its Subsidiaries because it is subject to restrictions, limitations or taxes on use or distribution either by contract or for regulatory or legal purposes, or is Cash and Cash equivalents that is collected from customers in advance, is being held on behalf of customers and represents a liability to such customers.

"Schedule" means the schedules to this Agreement, including the Disclosure Schedule.

"Second Molecule" has the meaning set forth in Section 2.9(k)(iv).

"Securities Act" means the Securities Act of 1933, as amended, and the rules and regulations promulgated thereunder, or any successor statute, rules or regulations thereto.

"Selected Independent Member" has the meaning set forth in Section 6.5(b).

"Selected Regulatory Expert" has the meaning set forth in Section 2.9(g)(i).

"Seller" has the meaning set forth in the Preamble.

"Seller Indemnified Parties" has the meaning set forth in Section 7.5(a).

"Seller Indemnifying Party" has the meaning set forth in Section 7.4.

"Seller Representative" has the meaning set forth in Section 9.1(a).

"Seller Representative's Account" means the bank account in the name of Thudaumot Holding B.V., with IBAN "NL21INGB0008522644" and BIC "INGBNL2A".

"Seller Transaction Expenses" means the aggregate amount of any and all fees and expenses incurred by or on behalf of, or paid or to be paid directly by, the Sellers, the Company or any Person that the Company pays or reimburses or is otherwise legally obligated to pay or reimburse (including any such fees and expenses incurred by or on behalf of the Sellers or the Seller Representative) in connection with the process of selling the Company or the negotiation, preparation or execution of this Agreement or the Ancillary Agreements or the performance or consummation of the transactions contemplated hereby or thereby, including (a) all fees and expenses of counsel, advisors including tax advisors, consultants, investment bankers,

accountants, auditors and any other experts in connection with the transactions contemplated hereby (including any process run by or on behalf of the Company in connection with such transactions), in excess of the $25,000 borne by the Buyer pursuant to Section 10.11; (b) any change in control, retention, transaction or severance payments that become payable to any director, manager, employee or individual consultant of the Company as a result of the transactions contemplated by this Agreement (including any such payments pursuant to "double trigger" arrangements resulting in payments and/or benefits provided upon a termination of service on or following the consummation of the Closing); (c) all other fees, disbursements, reimbursements, commissions, expenses or costs, in each case payable or incurred by the Company or Sellers in connection with the negotiation, preparation, and delivery of this Agreement and the consummation of the transactions contemplated by this Agreement; (d) any fees or expenses associated with obtaining the release and termination of any Liens in connection with the transactions contemplated hereby (including any process run by or on behalf of the Company in connection with such transactions); (e) all brokers', finders' or similar fees in connection with the transactions contemplated hereby (including any process run by or on behalf of the Company in connection with such transactions); (f) all Transfer Taxes incurred in connection with the transactions contemplated hereby; and (g) any applicable VAT or similar Tax due in connection with any item described in clauses (a) through (f); but in each case only to the extent any of the items set forth in clauses (a) through (g) above have not been paid prior to the Closing. For purposes of this Agreement and solely to avoid any double counting or duplication, any amounts to the extent actually taken into account in (i) the calculation of Company Debt will not be included in the calculation of Seller Transaction Expenses and (ii) the calculation of Seller Transaction Expenses will not be included in the calculation of Company Debt.

"Set-Off Account" has the meaning set forth in Section 7.11.

"Set-Off Rights" has the meaning set forth in Section 7.11.

"Shareholders' Agreement" means the shareholders' agreement relating to the Company executed between Thudaumot Holding B.V., Piet Wigerinck, Stichting Administratiekantoor Xinvento and the Company on May 6, 2022.

"Shares" has the meaning set forth in the Recitals.

"STAK" means Stichting Administratiekantoor Xinvento, a Dutch trust office foundation (*stichting*) having its corporate seat in Amsterdam, the Netherlands, and its address at Brouwersgracht 187H, 1015 GJ Amsterdam, registered with the trade register of the Dutch Chamber of Commerce under number 86127594.

"Straddle Period" shall mean any Tax period beginning before or on and ending after the Closing Date.

"Subsidiaries" means, with respect to any Person, a corporation or other entity of which fifty percent (50%) or more of the voting power of the securities is owned, directly or indirectly, by such Person.

"Subsidy" means any subsidies, grants, credits or rebates, including an R&D rebate (*S&O afdrachtvermindering*), in each case in the nature of Tax.

"Tax" or "Taxes" means any and all federal, state, local and foreign taxes of any jurisdiction, assessments and other governmental charges, social security contributions, including employer and employees social security contributions (*werknemersverzekeringen en volksverzekeringen*), any other contributions, duties, impositions and liabilities in the nature of a tax, including taxes based upon or measured by gross receipts, income, profits, gain, sales, use and occupation, value added, ad valorem, transfer, franchise, withholding, payroll, recapture, employment, alternative minimum, estimated, stamp, excise, escheat, unclaimed property and property taxes, together with all interest, penalties, damages, fines and additions imposed with respect to such amounts or such interest, penalties, damages, fines or additions and regardless of whether these items are chargeable directly or primarily against or attributable directly or primarily to any other Person. Grammatical variations of the term "Tax", such as "Taxable" or "Taxing", shall have correlative meanings.

"Tax Authority" means the IRS, the Dutch tax authority (*Belastingdienst*) and any other domestic or foreign Governmental Authority competent to impose any liability in respect of Taxes or responsible for the administration of any Taxes.

"Tax Contest" has the meaning set forth in Section 8.1.

"Tax Law" means any Legal Requirements (whether domestic or foreign) relating to Taxes.

"Tax Return" means any return, report or statement filed or required to be filed with respect to the determination, assessment or collection of any Tax or the administration of any Tax Laws (including any elections, declarations, schedules or attachments thereto, and any amendment or supplement thereof), including any information return, estimate, claim for refund, amended return or declaration of estimated Tax.

"Third-Party Claim" has the meaning set forth in Section 7.7(a).

"Trade Secret" means all trade secrets, know-how, inventions, methods, processes and processing instructions, technical data, specifications, research and development information, technology, product roadmaps, customer lists and any other information, in each case to the extent any of the foregoing derives economic value (actual or potential) from not being generally known to other persons who can obtain economic value from its disclosure or use.

"Transfer Taxes" means all use, transfer, recording, VAT, ad valorem, privilege, documentary, gross receipts, registration, conveyance, excise, license, stamp, deed or similar Taxes.

"Transferee" has the meaning set forth in Section 2.9(h).

"Undistributed and Earned Milestone Payments" has the meaning set forth in Section 7.9(a)(ii).

"Unresolved Claim" has the meaning set forth in Section 7.10(b).

"Unresolved Claim Amount" has the meaning set forth in Section 7.10(b).

"VAT" means (i) within the European Union, such Tax as may be levied in accordance with (but subject to derogations from) European Directive 2006/112/EC and (ii) outside the European Union, any Tax levied by reference to added value, sales or consumption.

"VAT Legislation" means all applicable VAT rules and regulations and orders thereunder.

1.2 Interpretation. For purposes of this Agreement, the following rules of interpretation apply:

(a) Descriptive Headings. The headings of the sections and paragraphs of this Agreement have been inserted for convenience of reference only and shall not be deemed to be part of this Agreement.

(b) Calculation of Time Period. Except as otherwise provided herein, when calculating the period of time before which, within which or following which any act is to be done or step taken pursuant to this Agreement, the date that is the reference date in calculating such period is excluded. If any period is to be measured in Business Days and the last day of such period is not a Business Day, the period in question ends on the next succeeding Business Day.

(c) Currency. Any reference in this Agreement to $ means U.S. dollars.

(d) Section and Similar References. Unless the context otherwise requires, all references in this Agreement to any "Section," "Schedule" or "Exhibit" are to the corresponding Section, Schedule or Exhibit of this Agreement.

(e) Mutual Drafting. The parties hereto have participated jointly in the negotiation and drafting of this Agreement and have been represented by their own legal counsel in connection with the transactions contemplated by this Agreement, with the opportunity to seek advice as to their legal rights from such counsel. In the event any ambiguity or question of intent or interpretation arises, this Agreement is to be construed as jointly drafted by the parties hereto and no presumption or burden of proof is to arise favoring or disfavoring any party by virtue of the authorship of any provision of this Agreement or by reason of the extent to which any such provision is inconsistent with any prior draft hereof.

(f) Counterparts. This Agreement may be executed in two (2) or more counterparts and by the different parties hereto on separate counterparts, each of which when so executed and delivered shall be an original, but all of which together shall constitute one and the same instrument.

(g) Electronic Delivery. The exchange of signature pages to this Agreement (in counterparts or otherwise) by electronic mail, .pdf scan or other electronic transmission (including via DocuSign) shall be sufficient to bind the parties to the terms and conditions of this Agreement.

(h) Other Definitional and Interpretive Matters. Unless otherwise expressly provided herein, for purposes of this Agreement, the following rules of interpretation shall apply:

(i) Exhibits/Schedules. The Exhibits and Schedules to this Agreement are hereby incorporated and made a part hereof and are an integral part of this Agreement. All

Exhibits and Schedules annexed hereto or referred to herein are hereby incorporated in and made a part of this Agreement as if set forth in full herein. The Company may, at its option, include in the Schedules items that are not material in order to avoid any misunderstanding, and such inclusion, or any references to dollar amounts, shall not be deemed to be an acknowledgement or representation that such items are material, to establish any standard of materiality or to define further the meaning of such terms for purposes of this Agreement or otherwise. Any matter, exception or qualification set forth in any section of any Schedule (including the Disclosure Schedule) shall be deemed to be referred to and incorporated in any other Schedule to the extent the relevance of such disclosure to such other Schedule is reasonably apparent on its face. Any capitalized terms used in any Schedule or Exhibit but not otherwise defined therein shall be defined as set forth in this Agreement. The inclusion of information in the Disclosure Schedule will not be construed as an admission to any third party of any liability or obligation of the Company or any Seller.

(ii) Gender and Number. Any reference in this Agreement to gender shall include all genders, and words imparting the singular number only shall include the plural and vice versa.

(iii) Herein. The words such as “herein,” “hereinafter,” “hereof,” and “hereunder” and any other words of similar import shall, unless otherwise stated, be construed to refer to this Agreement as a whole (including all of the Exhibits and Schedules to this Agreement) and not merely to a particular term or provision of this Agreement or subdivision in which such words appear unless the context otherwise requires.

(iv) Including. The word “including” or any variation thereof means “including, without limitation,” and shall not be construed to limit any general statement that it follows to the specific or similar items or matters immediately following it.

(v) Threatened. The word “threatened” or any variation thereof, unless otherwise described in the context in which it appears, means “threatened in writing or, to the Knowledge of the Sellers, otherwise.”

Section 2.
PURCHASE AND SALE

2.1 Sale and Purchase of the Shares. On the terms and subject to the conditions set forth in this Agreement, each Seller hereby, severally and not jointly, sells and agrees to transfer and deliver to Buyer, all of the Shares set forth opposite such Seller’s name on Schedule A and the Buyer hereby purchases the Shares from the relevant Seller.

2.2 Transfer of the Shares and Acknowledgement. On the terms and subject to the conditions set forth in this Agreement, the Sellers shall transfer the Shares on the Closing Date, free and clear from all Liens and together with all rights attached to the Shares, to the Buyer and the Buyer shall acquire and accept the Shares from the Sellers through the execution of a notarial deed of transfer (the “Deed of Transfer”). An agreed form of the Deed of Transfer is attached hereto as Schedule 2.2 (Form of Deed of Transfer). The Sellers shall procure that the Company acknowledges the transfer of the Shares on the Closing Date by co-signing the Deed of Transfer.

2.3 Ancillary Rights. The sale and transfer of the Shares include all ancillary rights attached thereto as per the Closing Date, such as the right to receive all distributions on the Shares that have been declared but not yet paid on the Closing Date.

2.4 Closing Date. On the terms and subject to the conditions set out in this Agreement and subject to Closing having taken place, the Shares and the Company including all its assets, liabilities and business, shall be for the risk and account (*voor rekening en risico*) of the Buyer as of the Closing Date.

2.5 Purchase Price; Adjustments.

(a) Purchase Price Payable at Closing. Subject to the terms and conditions set forth in this Agreement, the aggregate consideration payable by Buyer at the Closing to the Sellers for the Shares shall be an amount in cash equal to (the "Adjusted Purchase Price"):

(i) the Purchase Price;

(ii) plus the Estimated Closing Cash;

(iii) minus the Estimated Company Debt;

(iv) minus the Estimated Seller Transaction Expense;

(v) minus the Holdback Amount; and

(vi) minus the Advance Amount.

(b) Allocation. The Adjusted Purchase Price and the Milestone Payments, if any, shall be allocated among Sellers in accordance with the Distribution Methodology described in Schedule 2.5(c)(vi).

(c) Initial Closing Statement. At least three (3) Business Days prior to the anticipated Closing Date, the Company shall have delivered to Buyer a written statement (the "Initial Closing Statement") of the Company setting forth:

(i) An estimated balance sheet of the Company as of the close of business on the day immediately prior to the Closing Date, reflecting thereon the Company's estimate of all balance sheet items of the Company (the "Estimated Closing Balance Sheet");

(ii) a good-faith estimate of Company Debt (the "Estimated Company Debt"), together with a description and the amount of each element thereof;

(iii) a good-faith estimate of Closing Cash ("Estimated Closing Cash"), together with a description and the amount of each element thereof;

(iv) a good-faith estimate of the aggregate Seller Transaction Expenses (the "Estimated Seller Transaction Expenses"), together with a description and the amount of each element thereof;

(v) the resulting calculation of the Adjusted Purchase Price; and

(vi) the Distribution Methodology, which Distribution Methodology shall include (A) the amounts of the Adjusted Purchase Price and Milestone Payments, if any, allocated to each Seller in accordance with such Seller's Pro Rata Portion and (B) the amounts of any required withholding (if any) with respect to each Seller.

The Estimated Closing Balance Sheet, Estimated Company Debt and Estimated Closing Cash shall be prepared (i) in accordance with GAAP, consistently applied (except no footnotes shall be required), and using the same GAAP accounting principles, practices, methodologies and policies that were used to prepare the Financial Statements, provided that in the event of a conflict between GAAP and consistent application thereof in the Financial Statements, GAAP shall prevail and (ii) in accordance with the Company Governing Documents and any other Contract containing terms and conditions applicable to any payments to be made at Closing in connection with this Agreement, the Ancillary Agreements and the transactions contemplated hereby and thereby. The Initial Closing Statement (including the Distribution Methodology) shall be accompanied by a certificate of the Company's Chief Executive Officer certifying that (i) the Initial Closing Statement has been prepared, and all calculations of Estimated Company Debt, Estimated Closing Cash and Estimated Seller Transaction Expenses in the Initial Closing Statement have been made, in good faith in accordance with this Agreement and (ii) the Distribution Methodology is true, complete and correct in all respects on and as of the Closing Date.

Buyer shall be entitled to rely on the Initial Closing Statement as the true, correct, complete and definitive calculation of all amounts payable by Buyer pursuant to this Agreement at the Closing and thereafter (including each Seller's share of the Adjusted Purchase Price payable at Closing), and in no event shall Buyer or any of its Affiliates (including, after the Closing, the Company) have any liability to any Seller, any of their respective Affiliates or any other Person in respect of payments made at Closing or following the Closing in accordance with the terms of this Agreement as set forth on the Initial Closing Statement (including the Distribution Methodology).

(d) The Company and the Sellers shall provide promptly to Buyer and its Representatives all information and reasonable access to Company personnel as Buyer and its Representatives shall reasonably request in connection with its review of the Distribution Methodology and the Initial Closing Statement. Prior to Closing, the parties shall work in good faith to resolve any differences they may have with respect to the Initial Closing Statement.

(e) Post-Closing Adjustment to Purchase Price.

(i) As promptly as practicable, but in no event later than seventy-five (75) days following the Closing Date, Buyer shall in good faith prepare and deliver to the Seller Representative a statement (the "Closing Date Schedule") setting forth in reasonable detail (x) a consolidated balance sheet of the Company as of the close of business on the day immediately prior to the Closing Date, reflecting thereon Buyer's estimate of the same balance sheet items of the Company as included on the Estimated Closing Balance Sheet but adjusted to take into account the final balances as of the close of business on the day immediately prior to the Closing Date (the "Closing Balance Sheet") and (y) Buyer's calculation of, in each case as of the Adjustment Time, Company Debt, Closing Cash and

Seller Transaction Expenses. The Closing Date Schedule will entirely disregard (i) any and all purchase accounting effects on the assets or Liabilities of the Company as a result of the transactions contemplated hereby or of any financing or refinancing arrangements entered into at any time by the Buyer or any other transaction entered into by the Buyer in connection with the consummation of the transactions contemplated hereby (except to the extent set forth in the definitions of the terms Closing Cash, Company Debt and Seller Transaction Expenses), and (ii) any of the plans, transactions, or changes which the Buyer initiates or makes or causes to be initiated or made after the Closing with respect to the Company or its business or assets. Following the Closing, the Buyer shall provide the Seller Representative and its representatives timely reasonable access, during normal business hours and upon reasonable notice, to the records, properties, personnel and (subject to the execution of customary work paper access letters if requested) auditors of the Company relating to the preparation of the Closing Date Schedule and shall cause the personnel of the Company to cooperate with the Seller Representative in connection with its review of the Closing Date Schedule.

(ii) The Seller Representative may dispute any amounts reflected on the Closing Date Schedule by notifying the Buyer in writing of each disputed item, specifying the amount thereof in dispute and setting forth, in reasonable detail, the basis for such dispute, within thirty (30) days of Buyer's delivery to the Seller Representative of the Closing Date Schedule. If the Seller Representative delivers a notice of disagreement within such thirty (30) day period, the Seller Representative and Buyer shall, during the thirty (30) days following such delivery (or such longer period as they may mutually agree), each use reasonable efforts to reach an agreement on the disputed items or amounts in order to finally determine the amounts set forth on the Closing Date Schedule. If the Seller Representative and Buyer are unable to reach an agreement concerning any items on the Closing Date Schedule during such thirty (30) day period, they shall promptly thereafter (but in any event within ten (10) days) submit the dispute to the Accounting Arbitrator for resolution pursuant to Section (f).

(iii) The amounts set forth on the Closing Date Schedule shall be deemed conclusively determined for purposes of this Agreement upon the earlier to occur of (A) the failure of the Seller Representative to notify Buyer of a dispute within thirty (30) days of Buyer's delivery of the Closing Date Schedule as set forth in Section 2.5(e)(ii) above, (B) the mutual written resolution of all disputes pursuant to Section 2.5(e)(ii) by Buyer and the Seller Representative, and (C) the resolution of all disputes by the Accounting Arbitrator pursuant to Section 2.5(f).

(f) Adjustment Dispute Resolution.

(i) If the Seller Representative and Buyer are unable to reach agreement concerning the Closing Date Schedule pursuant to Section 2.5(e)(ii), they shall submit such dispute to an independent accounting or financial consulting firm of recognized national standing mutually selected by Buyer and the Seller Representative (the "Accounting Arbitrator"), for resolution pursuant to this Section 2.5(f) and instruct the Accounting Arbitrator to review the disputed items or amounts for the purpose of final determination of the amounts set forth on the Closing Date Schedule; provided that the Accounting

Arbitrator shall rely on GAAP, consistently applied, and using the same GAAP accounting principles, practices, methodologies and policies that were used to prepare the Financial Statements, provided that in the event of a conflict between GAAP and consistent application thereof in the Financial Statements, GAAP shall prevail. In making such determination and calculations, the Accounting Arbitrator shall consider only those items or amounts on the Closing Date Schedule as to which the Seller Representative has disagreed in writing. Each of Buyer and the Seller Representative shall promptly provide their assertions regarding the disputed amounts concerning the Closing Date Schedule pursuant to Section 2.5(e)(ii) in writing to the Accounting Arbitrator and to each other. The Accounting Arbitrator shall be instructed to function as an expert (*bindend adviseur*) and not as an arbitrator (*arbiter*) and to render its determination with respect to such disagreements as soon as reasonably practicable (which the parties hereto agree should not be later than thirty (30) days after submission of the dispute to the Accounting Arbitrator) a report setting forth the Accounting Arbitrator's calculation of the disputed amounts (which calculation shall be within the range of dispute in respect of each disputed item between the amounts set forth on the Closing Date Schedule and the notice of dispute delivered by the Seller Representative in accordance with Section 2.5(e)(ii)). The Accounting Arbitrator shall base its determination solely on the written submissions of the parties and shall not conduct an independent investigation. Absent fraud or manifest error, such report shall be final and binding upon the Seller Representative, Sellers and Buyer and the resulting Closing Date Schedule and amounts set forth thereon shall be final for all purposes of this Agreement. The Buyer, on the one hand, and the Seller Representative (on behalf of Sellers), on the other hand, shall each pay their own fees and expenses.

(ii) The fees, costs and expenses of the Accounting Arbitrator shall be allocated to and borne by the Buyer and the Seller Representative, on behalf of Sellers, based on the inverse of the percentage that the Accounting Arbitrator determination (before such allocation) bears to the total amount of the total items in dispute as originally submitted to the Accounting Arbitrator. For example, should the items in dispute total in amount to one thousand dollars ($1,000) and the Accounting Arbitrator awards six hundred dollars ($600) in favor of the Seller Representative's position, sixty percent (60%) of the costs of its review would be borne by Buyer and forty percent (40%) of the costs would be borne by the Seller Representative, on behalf of the Sellers.

(iii) Buyer, the Company, the Seller Representative and the Sellers agree that the procedure set forth in this Section 2.5(f) for resolving disputes with respect to the Closing Date Schedule shall be the sole and exclusive method for resolving any such disputes.

(g) Payment Upon Final Determination of Adjustments.

(i) If (A) the Closing Cash less the sum of Company Debt and Seller Transaction Expenses, as finally determined in accordance with this Section 2.5, is less than (B) the sum of the Estimated Closing Cash less Estimated Company Debt and Estimated Seller Transaction Expenses, as estimated in accordance with Section 2.5(c) (such deficiency, the "Purchase Price Surplus"), then (x) a portion of the Holdback Amount equal to the absolute value of the Purchase Price Surplus shall be forfeited and retained by

Buyer and (y) if the Holdback Amount is insufficient to satisfy the Purchase Price Surplus, Buyer shall have the right, but not the obligation, to set off, in whole or in part, any Purchase Price Surplus amounts owed to Buyer in excess of the Holdback Amount against any obligation or payment it owes to any Seller (including, for the avoidance of doubt, any unpaid Milestone Payments) or require the Sellers to pay the outstanding Purchase Price Surplus to Buyer in accordance with their Pro Rata Portion within ten (10) Business Days.

(ii) If (A) the Closing Cash less the sum of Company Debt and Seller Transaction Expenses, as finally determined in accordance with this Section 2.5, is greater than (B) the Estimated Closing Cash less the sum of Estimated Company Debt and Estimated Seller Transaction Expenses, as estimated in accordance with Section 2.5(c) (such excess, the "Purchase Price Deficiency"), then an amount equal to the Purchase Price Deficiency shall be paid by the Buyer to the Seller Representative (for further distribution to the Sellers in accordance with the Distribution Methodology).

(iii) For the avoidance of doubt, the remainder of the Holdback Amount after payments, if any, made pursuant to Section 2.5(g)(i) shall continue to be retained by Buyer and released in accordance with Section 7.10.

(iv) Any payments made to any party pursuant to this Section 2.5 shall, to the extent permitted by applicable Tax Law, constitute an adjustment of the Adjusted Purchase Price for Tax purposes and shall be treated as such by Buyer and Sellers on their Tax Returns.

(h) Withholding Rights; Deductions from Purchase Price. Each of the Company and Buyer (and any of their respective paying agents and Affiliates) shall be entitled to deduct and withhold from any payment to any Person under this Agreement such amounts as any of them is required to deduct and withhold with respect to such payments. To the extent that amounts are so withheld or deducted and timely paid to the appropriate Tax Authority, such amounts shall be treated for all purposes of this Agreement as having been paid to the Person in respect of which such deduction and withholding was made.

2.6 Closing.

(a) Time and Place. Closing shall take place at the offices of the Notary immediately after the signature of this Agreement (the "Closing"). The date on which the Closing occurs is sometimes referred to herein as the "Closing Date".

(b) Transactions at the Closing.

(i) Payment of Company Debt; Transaction Expenses. Upon the Closing, Buyer shall fund the Company to enable the Company to pay or cause to be paid, (A) all Estimated Company Debt (other than the Convertible Loan Repayment Amounts as described in Section 2.6(b)(iv) below) payable to third parties evidenced on the Initial Closing Statement, by wire transfer of immediately available funds, and (B) the Estimated Seller Transaction Expenses identified on the Initial Closing Statement by wire transfer of immediately available funds to the respective vendors or other Persons and in the respective amounts set forth thereon.

(ii) Payment of Adjusted Purchase Price to Seller Representative (on behalf of the Sellers). Upon the Closing, Buyer shall pay or cause to be paid by wire transfer into the Seller Representative's Account the Adjusted Purchase Price in respect of the Shares being sold to Buyer by Sellers at the Closing.

(iii) Payment of Advance Amount to the Seller Representative. Buyer shall pay or cause to be paid the Advance Amount to the Seller Representative, as provided in Section 9.1(f) below.

(iv) Repayment of the Convertible Loan Amounts. Upon the Closing, Buyer shall pay, or cause to be paid to, the Company an amount equal to $2,359,560 to pay to the Convertible Loan Holders the aggregate Convertible Loan Repayment Amounts. The Company hereby undertakes that it will, on or as soon as practicable following the Closing Date, use the Convertible Loan Repayment Amounts to satisfy its obligations vis-à-vis the Convertible Loan Holders under the Convertible Loan Agreements in full.

(v) Each such payment made at the Closing pursuant to Section 2.6(b)(i) – (iv) above shall be made by wire transfer of immediately available funds; provided that prior to the Closing, the Seller's Representative shall provide Buyer with valid wiring instructions.

(vi) Execution of the Deed of Transfer. Upon (i) confirmation by the Seller Representative (on behalf of the Sellers) of having received the Adjusted Purchase Price and (ii) the instruction by e-mail provided for in Sections 2.7(k) and 2.8(c) below, the Notary will execute the Deed of Transfer.

(vii) The STAK hereby undertakes that it will, upon receipt of its relevant part of the (Adjusted) Purchase Price, make available and arrange for payment to each relevant depositary receipt holder of such part of the (Adjusted) Purchase Price a depositary receipt holder is entitled to, pursuant to and in accordance with article the STAK's administration conditions.

(viii) By virtue of this Agreement and as partial security for the purchase price adjustments set forth in Section 2.5(g) and the indemnity obligations set forth in Section 7.4 hereof, at the Closing, Buyer will retain and hold back the Holdback Amount. Until and unless the Holdback Amount is released to the Sellers or forfeited to Buyer pursuant to Section 2.5(g) or Section 7.10, the Sellers shall, and do, hereby pledge and grant a security interest in the Holdback Amount to Buyer on its own behalf and on behalf of the other Buyer Indemnified Parties.

2.7 Closing Deliverables of Sellers. At or prior to the Closing, Sellers shall deliver, or cause to be delivered, to Buyer the following:

(a) each Ancillary Agreement, duly executed and delivered by Sellers and the Seller Representative (in each case, if party thereto), in the form agreed by the parties and attached as an Exhibit hereto (if applicable);

(b) a certificate of the Chief Executive Officer of the Company, dated as of the Closing Date, in form and substance reasonably satisfactory to Buyer, certifying as to (i) the copies of the Company Governing Documents, each as in effect as of immediately prior to the Closing, and (ii) the actions taken by the shareholders of the Company authorizing certain actions contemplated by this Agreement and certain other Ancillary Agreements to which the Company may be party or subject, and the other transactions contemplated thereby, copies of which actions shall be attached to such certificate;

(c) resignations, dated the Closing Date, of the sole managing director of the Company;

(d) the execution of the written shareholders' resolution of the Company appointing new management board members for the Company as per the execution of the Deed of Transfer;

(e) a duly executed IRS Form W-8 from each Seller;

(f) the Initial Closing Statement required to be delivered to Buyer pursuant to Section 2.5(c);

(g) written evidence, in form and substance reasonably satisfactory to Buyer, of the termination of the following agreements: (i) the Shareholders' Agreement; (ii) that certain Consultancy Agreement, dated June 27, 2022, by and between the Company and Murray Stewart; and (iii) that certain Employment Agreement, dated April 1, 2022, by and between the Company and Sarah Hafith;

(h) written evidence, in form and substance reasonably satisfactory to Buyer, of the confirmatory assignment of intellectual property ownership and rights from each of (i) Piet Wigerinck, (ii) Betrand Vivet and (iii) NovAliX S.A.S.;

(i) an employment agreement, in form and substance reasonably satisfactory to Buyer, with Claudine van der Sande and a settlement agreement on the basis of which the Management Agreement with Thudaumot Holding B.V., dated July 12, 2022, terminates with mutual consent;

(j) an addendum to the Consultancy Agreement with Wigerinck Consulting B.V., dated June 27, 2022, in form and substance reasonably satisfactory to Buyer;

(k) duly executed, legalized and apostilled (where applicable) powers of attorney by each Seller in favor of the Notary, authorizing the Notary to execute, on its behalf, the Deed of Transfer and an e-mail instruction to the Notary by the Seller Representative on behalf of the Sellers and the Company that the Notary may proceed with the execution of the Deed of Transfer;

(l) duly executed, legalized and apostilled (where applicable) powers of attorney by the Company in favor of the Notary, authorizing the Notary to execute, on its behalf, the Deed of Transfer;

(m) waiver and release, in form and substance reasonably satisfactory to Buyer and attached hereto as Exhibit A, evidencing the Convertible Loan Holders set forth in Schedule 2.7(m) have consented to repayment of the Convertible Loan Agreements by payment by the Company of the Convertible Loan Repayment Amount in accordance with Section 2.6(b)(iii); and

(n) evidence of revocation of any existing proxy (*volmacht*) held by any representative of the Company (other than a power of attorney to execute the Deed of Transfer, if applicable).

2.8 Closing Deliverables of Buyer. At or prior to the Closing, Buyer shall deliver, or cause to be delivered, to the Seller Representative, the Sellers or the Notary, as applicable, the following:

(a) the Adjusted Purchase Price payable in accordance with Section 2.6(b)(ii); and

(b) each other Ancillary Agreement to which Buyer is a party, duly executed and delivered by Buyer; and

(c) a duly executed, legalized and apostilled (where applicable) power of attorney by the Buyer in favor of the Notary, authorizing the Notary to execute, on its behalf, the Deed of Transfer and an e-mail instruction to the Notary by the Buyer that the Notary may proceed with the execution of the Deed of Transfer.

2.9 Milestone Payments

(a) Milestone Events. Upon the first occurrence of any of the events set forth in the table below under "Milestone Event" (items (i) through (xii) below, each a "Milestone"), Buyer shall promptly (and in any event, no later than ninety (90) Business Days thereafter) deliver a written notice (a "Milestone Achievement Notice") to the Seller Representative of such occurrence and, within ten (10) Business Days of such Milestone Achievement Notice, deposit or cause to be deposited the amount of cash in U.S. Dollars set forth in the table below under "Milestone Payment" opposite such Milestone (each, a "Milestone Payment") with the Seller Representative, for further distribution to the Sellers, in accordance with the Distribution Methodology, in each case subject to any Set-Off Rights pursuant to Section 7.11.

Milestone Event	Milestone Payment
(i) Commencement of GLP toxicology trials for the Lead Candidate;	$2,000,000
(ii) Filing of an IND application for the Lead Candidate;	$4,000,000
(iii) Receipt of approval in the United States for the Lead Candidate;	$15,000,000
(iv) Receipt of approval in the European Union for the Lead Candidate;	$10,000,000
(v) Receipt of approval in the United States for a second indication for either the Lead Candidate or a Second Molecule;	$15,000,000
(vi) Receipt of approval in the European Union for a second indication for either the Lead Candidate or the Second Molecule;	$10,000,000

Milestone Event	Milestone Payment
(vii) Achievement of $250,000,000 in aggregate worldwide annual Net Sales generated by one or more indications for which the Lead Candidate is approved;	$15,000,000
(viii) Achievement of $500,000,000 in aggregate worldwide annual Net Sales generated by one or more indications for which the Lead Candidate is approved;	$25,000,000
(ix) Achievement of $1,000,000,000 in aggregate worldwide annual Net Sales generated by one or more indications for which the Lead Candidate is approved;	$35,000,000
(x) Achievement of $250,000,000 in aggregate worldwide annual Net Sales generated by one or more indications for which the Second Molecule is approved;	$15,000,000
(xi) Achievement of $500,000,000 in aggregate worldwide annual Net Sales generated by one or more indications for which the Second Molecule is approved; and	$25,000,000
(xii) Achievement of $1,000,000,000 in aggregate worldwide annual Net Sales generated by one or more indications for which the Second Molecule is approved.	$35,000,000

(b) Sale of Company or its Assets. At any time prior to the payment of the Milestone Payments to Seller Representative (on behalf of the Sellers) (or a final determination that no further Milestone Payments are or may be payable to Seller Representative (on behalf of the Sellers)), if Buyer effects either (x) a sale, lease, exchange or other transfer, directly or indirectly, in one transaction or a series of related transactions, of all or substantially all of the assets (which assets shall include, for the avoidance of doubt, the Company Know-How) of the Company to a third-party buyer, which third-party buyer shall specifically exclude the Buyer, the Company or any affiliate or wholly-owned subsidiary of Buyer or the Company (a "Third-Party Purchaser"), or (y) a merger, consolidation, recapitalization or other transaction in which any Third-Party Purchaser becomes the beneficial owner, directly or indirectly, of 50% or more of the combined voting power of all interests in the Company, Buyer shall make provision for the transferee, lessee or successor to assume and succeed to the obligations of Buyer in, subject to the limitations and other provisions set forth in, this Section 2.9; provided, that, if no such provision for assumption of the obligations of Buyer in this Section 2.9 has been made, Buyer shall remain responsible for all of its obligations with respect to the Milestone Payments set forth in subsection (a) hereof, subject to the limitations and other provisions set forth in this Section 2.9. Seller Representative shall, upon the request of Buyer, cooperate in good faith with Buyer and the Third-Party Purchaser in the execution and delivery of such documents as shall reasonably be required to consummate such transactions.

(c) Certain Limitations.

(i) The Milestones set forth in Section 2.9(a)(i) – (a)(vi) (each, a "Regulatory Milestone" and collectively, the "Regulatory Milestones") shall be payable no more than

once. The Milestones set forth in Section 2.9(a)(vii) – (a)(xii) (each, a "Net Sales Milestone" and collectively, the "Net Sales Milestones") shall be payable no more than once, for up to the aggregate Milestone Payments under Section 2.9(a)(vii) – (a)(xii) of $150,000,000. For the avoidance of doubt, (1) each of the Regulatory Milestone Payments shall become payable upon the occurrence of the associated Milestone, irrespective of the order in which the Milestones occur relative to each other and (2) the total Milestone Payments that may be made pursuant to this Section 2.9 shall not exceed $206,000,000 in the aggregate.

(ii) Buyer shall have no obligation to pay the Milestone Payments set forth in Section 2.9(a)(iii) or (v): (x) prior to the issuance of a United States patent relating to the Company Know-How, wherein such United States patent contains claims covering the Lead Candidate or Second Compound (as applicable) and such United States patent is issued to or controlled by Buyer or Affiliate thereof, provided, that, subject to the satisfaction of all other conditions for payment set forth in this Agreement, payment of the Milestone Payments set forth in Section 2.9(a)(iii) or (v) shall be paid within ten (10) Business Days after the issuance of such United States patent, or (y) following the expiration of the last to expire United States patent or the finding of invalidity or unenforceability of such United States patent.

(iii) Buyer shall have no obligation to pay the Milestone Payments set forth in Section 2.9(a)(iv) or (vi): (x) prior to the issuance of a European patent relating to the Company Know-How, wherein such European patent contains claims covering the Lead Candidate or Second Compound (as applicable) and such European patent is issued to or controlled by Buyer or Affiliate thereof, provided, that, subject to the satisfaction of all other conditions for payment set forth in this Agreement, payment of the Milestone Payments set forth in Section 2.9(a)(iv) or (vi) shall be paid within ten (10) Business Days after the issuance of such European patent, or (y) following the expiration of the last to expire European patent or the finding of invalidity or unenforceability of such European patent.

(d) Post-Closing Obligations.

(i) Solely with respect to the Regulatory Milestones, during the period beginning on the Closing Date and ending on the earlier of (x) the approval of the Lead Candidate in either the United States or the European Union, and (y) the shelving of the Lead Candidate for CHI in accordance with Section 6.5(c), the Buyer shall use commercially reasonable efforts, consistent with the efforts normally undertaken by a similarly-situated company with respect to products in similar stages of development and with similar commercial potential, to achieve such Regulatory Milestones.

(ii) Following the Closing, Buyer shall use commercially reasonable efforts, consistent with the efforts normally undertaken by a similarly-situated company with respect to products in similar stages of development and with similar commercial potential, to (x) take such actions consistent with the Development Plan, attached as Exhibit B hereto, and (y) allocate an annual budget for the development of the Products of not less than (1) an average of EUR 200,000 per month in the first year following the Closing Date and (2)

such amount reasonably determined by Buyer and its Affiliates in the second year following the Closing Date.

(iii) Without limiting the generality of the foregoing, Buyer shall not, and shall cause the Company not to, take any actions with the purpose of hindering or frustrating the achievement or payment of any Milestones hereunder in a timely manner.

(iv) The covenants and obligations expressly set forth in this Section 2.9(d) constitute the sole and exclusive covenants and obligations of the Buyer and the Company with respect to the Milestones, and no other covenant or obligation not otherwise set forth in this Section 2.9(d) shall be construed to apply to the Milestones.

(e) Post-Closing Operations. After the Closing, but subject to and without limiting the express obligations of Buyer under Section 2.9(d), Buyer shall have sole discretion over all matters relating to the Lead Candidate, the Second Molecule and Products, the operation of the Company's respective businesses and the use of the assets, properties and interests of the Company, including all matters relating to the development, manufacturing, commercialization of, patent coverage of, or pursuit of or obtaining regulatory approval for, any Product (including whether to pursue regulatory approval of any Product) and to the allocation of personnel and other resources reasonably available to the Company (including decisions with respect to sales strategies, pricing, distribution, marketing, budgeting, allocation of resources and personnel and including any decisions to discontinue the operations of the Company's business, in whole or in part, or the discontinuation of the pursuit of any product development, regulatory approval, or commercial activities) worldwide. Without limiting any express obligation of Buyer pursuant to Section 2.9(d), after the Closing, Buyer is under no obligation to operate the businesses of the Company to maximize the achievement of any Milestone Payment. The parties further acknowledge and agree that there is no assurance that any Milestone Payment will be realized by the Sellers and that none of Buyer, its Affiliates or any Representative thereof has promised or projected any specific amount. None of Buyer, its Affiliates or any Representative thereof owes any fiduciary duty to the Company or any Seller with respect to the Milestone Payments. Further, the parties acknowledge that Buyer's sole obligations with respect to any potential Milestone Payments are expressly set forth in this Section 2.9 and Buyer and the Sellers hereby waive any implied covenants or obligations, including the implied covenant of good faith and fair dealing.

(f) Information Right in Respect of Milestones. After the Closing through and until such time that all Milestones have been achieved (or a final determination that no further Milestones may be achieved), no later than one hundred twenty (120) days after each fiscal year, the Company shall provide the Seller Representative, acting on behalf of the Sellers, with material information reasonably requested by Seller Representative (provided, that, such information reasonably requested by Seller Representative shall constitute information that is not otherwise available to Claudine van der Sande in her capacity as a service provider to the Company, Buyer or their Affiliates), which request shall be received by the Company no later than thirty (30) days after such fiscal year, for the sole purpose of determining whether one or more Milestones has occurred. Notwithstanding anything to the contrary in this Section 2.9(f), the Company shall not be obligated to provide the Seller Representative with any information pursuant to this Section 2.9(f) to the extent that (i) such information is a Trade Secret, (ii) the disclosure of any such information would result in the loss of attorney-client privilege between the Company (and its

Affiliates, including Buyer) and its counsel; or (iii) the Company or Buyer determines in good faith, after consulting with counsel and the Seller Representative, that provision of such access or information would violate any applicable Law; provided, however, that the Company shall use commercially reasonable efforts to implement alternative arrangements to provide the Seller Representative alternative means of obtaining such access or information to the fullest extent practicable without risking loss of privilege or protections under, or risking a violation of, such applicable Law or privilege (including for example, redactions, summaries of information, etc.).

(g) Dispute Resolution.

(i) If the Seller Representative believes that any Regulatory Milestone has occurred, or that any Milestone Achievement Notice related to any Regulatory Milestone ("Regulatory Milestone Achievement Notice") is inaccurate in whole or in part, then the Seller Representative shall promptly deliver a written notice thereof (a "Regulatory Milestone Dispute Notice"), in reasonable detail, to Buyer; provided, however, that any Regulatory Milestone Achievement Notice shall become final and binding upon the parties forty-five (45) days following delivery thereof, unless prior to such date the Seller Representative delivers a Regulatory Milestone Dispute Notice to Buyer. During the thirty (30) days following the delivery of a Regulatory Milestone Dispute Notice, Buyer and the Seller Representative shall attempt in good faith to resolve any dispute as to whether any Regulatory Milestone has occurred and whether any Milestone Payment is payable for any Regulatory Milestone. If the parties do not reach agreement with respect to any dispute relating to any such matter within thirty (30) days after a Regulatory Milestone Dispute Notice is delivered to Buyer, the parties shall submit for arbitration all matters that remain in dispute and that were properly included in the Regulatory Milestone Dispute Notice to a disinterested individual who has appropriate scientific, technical and regulatory expertise (as relevant) to resolve any disputes referred to him or her under this Agreement (a "Regulatory Expert") who is mutually agreed to by Buyer and the Seller Representative. If Buyer and the Seller Representative cannot agree on a mutually acceptable Regulatory Expert within thirty (30) days after either party has determined that the parties cannot reach agreement with respect to a dispute, then within five (5) Business Days after the expiration of such thirty (30) day period, each of Buyer and the Seller Representative shall appoint one Regulatory Expert who shall jointly select a third Regulatory Expert within five (5) Business Days after the last to occur of their respective appointments to resolve the referred matter. The Regulatory Expert mutually agreed by the parties or, if the parties cannot agree, the third Regulatory Expert selected by the party-appointed Regulatory Experts is referred to as the "Selected Regulatory Expert". Buyer and the Seller Representative shall instruct the Selected Regulatory Expert to determine as promptly as practicable but in no event later than thirty (30) days after such Person's appointment (the "Determination Period") whether the disputed Regulatory Milestone has occurred. The Selected Regulatory Expert's determination shall be made based on the submission of documents by the parties unless the Selected Regulatory Expert determines that an oral hearing is necessary. The Selected Regulatory Expert shall determine that which shall be conclusively deemed to be fair and appropriate deadlines for submitting documents and dates, if any, of oral hearings. Each of Buyer and the Seller Representative shall pay its own expenses of arbitration. The fees, costs and expenses of the Selected Regulatory Expert shall be borne in full by Buyer or the Seller Representative (on behalf of the Sellers) whose assertion was not accepted by the

Selected Regulatory Expert. Any decision rendered by the Selected Regulatory Expert shall be final and binding upon the parties. All proceedings conducted by the Selected Regulatory Expert shall take place in Boston, Massachusetts.

(ii) If the Seller Representative believes that any Net Sales Milestone has occurred or that any Milestone Achievement Notice relating to any Net Sales Milestone ("Net Sales Achievement Notice") is inaccurate in whole or in part, then the Seller Representative shall promptly deliver written notice (a "Net Sales Dispute Notice") thereof, in reasonable detail, to Buyer; provided, however, that any Net Sales Achievement Notice shall become final and binding upon the parties forty-five (45) days following delivery thereof, unless prior to such date the Seller Representative delivers a Net Sales Dispute Notice to Buyer. During the thirty (30) days following the delivery of a Net Sales Dispute Notice, Buyer and the Seller Representative shall attempt in good faith to resolve any dispute as to the occurrence of any Net Sales Milestone or the accuracy of any Net Sales Milestone Achievement Notice. If the parties do not reach agreement with respect to any dispute relating to any such matter within thirty (30) days after a Net Sales Milestone Dispute Notice is delivered to Buyer by the Seller Representative, the parties shall submit for arbitration all matters that remain in dispute and that were properly included in the Net Sales Dispute Notice to an internationally nationally recognized independent accounting firm (the "Accounting Expert"). The Accounting Expert shall be a nationally recognized independent public accounting firm as shall be agreed upon by the parties in writing or, if the parties are unable to so agree in writing within thirty (30) days, then Buyer and the Seller Representative shall each select such a firm and such firms shall jointly select a third nationally recognized independent public accounting firm to serve as the Accounting Expert. The parties shall jointly instruct the Accounting Expert that it shall (i) review only the matters that were properly included in the Net Sales Dispute Notice and which remain in dispute, (ii) make its determination in accordance with the requirements of this Section 2.9(g)(ii) and (iii) render its written decision as promptly as practicable but in no event later than thirty (30) days after submission to the Accounting Expert of all matters in dispute. The Accounting Expert's determination shall be accompanied by a certificate of the Accounting Expert that it reached its decision in accordance with the provisions of this Section 2.9(g)(ii). Each of Buyer and the Seller Representative shall pay its own expenses of arbitration. The fees, costs and expenses of the Accounting Expert shall be allocated to and borne by Buyer and the Seller Representative (on behalf of the Sellers) based on the inverse of the percentage that the Accounting Expert's determination (before such allocation) bears to the total amount of the total items in dispute as originally submitted to the Accounting Expert. For example, should the items in dispute total in amount to one thousand dollars ($1,000) and the Accounting Expert awards six hundred dollars ($600) in favor of the Seller Representative's position, sixty percent (60%) of the costs of its review would be borne by Buyer and forty percent (40%) of the costs would be borne by the Seller Representative, on behalf of the Sellers. Any decision rendered by the Accounting Expert shall be final and binding upon the parties. All proceedings conducted by the Accounting Expert shall take place in Boston, Massachusetts. Any underpayments of Milestone Payments relating to the Regulatory Milestones or the Net Sales Milestones shall be paid by Buyer within forty-five (45) days of notification of the results of such decision. Any overpayments of Milestone Payments relating to the Regulatory Milestones or Net Sales Milestones shall be fully creditable by Buyer against any amounts subsequently payable

by Buyer pursuant to this Agreement or, if no such amounts become payable within ninety (90) days after notification of such results, shall be refunded by the Sellers to Buyer or its designee.

(h) Permitted Transfers. The interests of any Seller in any Milestone Payment shall not be assignable or transferable, except: (a) by operation of law; (b) in connection with a Permitted Transfer (as defined below) (the assignee or transferee of any assignment or transfer permitted pursuant to this Section 2.9(h) being referred to as a "Transferee"); provided, however, that no assignment or transfer of any such interest may occur pursuant to this Section 2.9(h) unless (x) all of such Seller's interests in all Milestone Payments are transferred to the proposed Transferee, (y) such Seller (or its Representative authorized to act on Seller's behalf) signs a transfer or assignment agreement, in a form reasonably acceptable to Seller Representative and Buyer, irrevocably transferring or assigning all such interests in all Milestone Payments to the proposed Transferee, and (z) such proposed Transferee signs or delivers to the Buyer and Seller Representative a counterpart to this Agreement agreeing to be bound by all of the terms hereof (it being understood that any attempted assignment or transfer in violation this sentence shall be null and void). For purposes of this Section 2.9(h), "Permitted Transfer" shall mean any transfer: (A) if a Seller is an individual, upon the death of such holder pursuant to any will, trust or similar instrument or pursuant to the laws of descent and distribution; or (B) if a Seller is a corporation, trust, partnership or limited liability company, to one or more shareholders, beneficiaries, partners or members of such holder. For the avoidance of doubt, Buyer shall have no liability in respect of any transfer or assignment effected in accordance with this Section 2.9(h), including in respect of any payment of Milestone Payments to the Seller Representative (for further distribution to the Sellers (including the Transferee) in accordance with the Distribution Methodology).

(i) Confidentiality. From and after the Closing, the Seller Representative and each Seller shall (and shall cause such Seller's Affiliates and Representatives to) hold in confidence all information provided to each such Person pursuant to this Section 2.9 and shall not disclose to any other Person, or use, any such information, directly or indirectly, except to the extent (i) such information has become available to the public generally or is generally known in the industry, other than by acts by the Seller Representative or such Seller or any such Person's Representatives in violation of this Agreement, (ii) necessary to enforce the Sellers' or the Seller Representative's rights hereunder or (iii) required by law or legal process, or pursuant to any subpoena or order to be disclosed; provided, that, prior to making any such disclosure in the case of the foregoing clause (iii), such Seller or the Seller Representative, as applicable, to the extent legally permissible, shall provide reasonable advance notice to Buyer and reasonable assistance to Buyer (at Buyer's sole cost and expense) in attempting to obtain a protective order or other appropriate remedy concerning such disclosure.

(j) No Security. Without limiting anything in this Agreement, the right of any Seller to receive such Seller's portion of any Milestone Payments (i) does not give such Seller dividend rights, voting rights, liquidation rights, preemptive rights or other rights, in each case, of holders of capital shares of the Company, (ii) shall not be evidenced by a certificate or other instrument, (iii) shall not be assignable or otherwise transferable by such Seller except in accordance with Section 2.9(h), (iv) shall not accrue or pay interest on any portion thereof and (v) does not represent any right other than the right to receive the consideration set forth in this Agreement.

(k) Certain Definitions.

(i) "Lead Candidate" means the first molecule selected by Buyer, in its sole discretion, for the commencement of GLP toxicology studies, which (i) behaves as a KATP channel opener or targets SUR1/Kir6.2 and (ii) is described generically or specifically in the Registered Company Patents or the Company Know-How (or described generically or specifically in a patent or application claiming priority to the Registered Company Patents or the Company Know-How). For the avoidance of doubt, the selection of the Lead Candidate shall occur substantially concurrently with the Milestone set forth in Section 2.9(a)(i).

(ii) "Net Sales" means the worldwide gross sales of Products which are actually received by Buyer, the Company, and their Affiliates and sublicensees in such period, less the following deductions which are actually incurred, allowed, paid, accrued or specifically allocated to such worldwide gross sales amounts of such Products: (a) credits or allowances actually granted for damaged Product, returns or rejections of Product, price adjustments and billing errors; (b) governmental and other rebates (or equivalents thereof) granted to managed health care organizations; pharmacy benefit managers (or equivalents thereof); federal, state/provincial, local and other governments, their agencies and purchasers and reimbursors; or to trade customers; (c) normal and customary trade, cash and quantity discounts, allowances and credits; (d) distribution services agreement fees allowed or paid to third party distributors; (e) transportation costs, including insurance, for outbound freight related to delivery of Products to the extent included in the gross amount invoiced; (f) sales taxes, value added taxes and other Taxes (excluding for the avoidance of doubt income Taxes of the Company, Buyer and its Affiliates) applied to the sale of a Product to the extent included in the gross amount invoiced; and (g) any other items that reduce gross sales amounts as required by GAAP in the United States applied on a consistent basis. Sales of a Product between or among Buyer, the Company, and their Affiliates, licensees, or sublicensees will be excluded from the computation of Net Sales, but the first subsequent sale of such Product by Buyer, the Company or their Affiliates, licensees, or sublicensees to a Person that is not Buyer, the Company or their Affiliate, licensee, or sublicensee, will be included in the computation of Net Sales.

(iii) "Product" means each of the Lead Candidate and Second Molecule.

(iv) "Second Molecule" means a molecule, other than the Lead Candidate, which (i) behaves as a K_{ATP} channel opener or targets SUR1/Kir6.2 and (ii) is described generically or specifically in the Registered Company Patents or the Company Know-How (or described generically or specifically in a patent or application claiming priority to the Registered Company Patents or the Company Know-How).

2.10 Deemed Payment.

The payments actually made by Buyer, or on its behalf, to the Seller Representative pursuant to this Agreement shall be subject to the conditions and contingencies of this Agreement, as applicable, and treated for all purposes as full satisfaction of Buyer's payment obligations under this Agreement.

Section 3.
REPRESENTATIONS AND WARRANTIES REGARDING THE COMPANY

The Sellers hereby, jointly and not severally, based on their Pro Rata Portion, represent and warrant to Buyer that the statements in this Section 3 are true, complete and correct as of the date of this Agreement (unless the particular statement speaks expressly as of another date, in which case it is true, complete and correct as of such other date), subject, in any case, to the exceptions provided in the disclosure schedule supplied by the Sellers to Buyer, dated as of the date of this Agreement (the "Disclosure Schedule").

3.1 Organization and Good Standing; Organizational Documents.

(a) The Company is a private limited liability company (*besloten vennootschap met beperkte aansprakelijkheid*) incorporated under the laws of the Netherlands. The Company is duly organized and validly existing under the laws of its jurisdiction of formation and has all requisite corporate or similar power and authority to own, lease and operate its properties and assets and to carry on its business as now being conducted and as proposed to be conducted and is duly qualified to do business under the laws of the jurisdiction in which it conducts its business, except where the failure to be so qualified or authorized has not had a Material Adverse Effect.

(b) Prior to the date of this Agreement, the Company has furnished to Buyer true, correct and complete copies of the Company Governing Documents. Such documents are in full force and effect, and the Company is not in material violation of any provision of its Company Governing Document.

(c) The Company (i) has always kept its books and (ii) meets all registration requirements in accordance with Legal Requirements. The administration and bookkeeping of the Company are accurate and complete, have been maintained properly and are capable of providing adequately detailed information as to the Company's financial position at any time.

(d) The Company has properly kept record of all meetings of shareholders, managing directors and supervisory directors and the minutes of these meetings fully and correctly reflect the matters which have been dealt with during those meetings.

(e) The Company has no and has not had any branches or interests in other persons. The Company is not a group company (*groepsmaatschappij*) of any other company and it is not a party to any partnership agreement (*vennootschap onder firma*, *commanditaire vennootschap*, *maatschap* or equivalent under any applicable Legal Requirements).

3.2 Capitalization and Ownership of Shares.

(a) Section 3.2(a) of the Disclosure Schedule sets forth, for the Company, the amount of its authorized share capital, if applicable, other equity or ownership interests, the amount of its outstanding capital stock or other equity or ownership interests outstanding, and the names and addresses of the record and beneficial owners of its outstanding capital stock or other equity or ownership interest. The Shares owned by the Sellers constitute the entire issued and outstanding share capital of the Company. No Shares (or any other capital stock or other equity or ownership interests of the Company) are reserved for issuance, or will be reserved for issuance as of the

Closing Date. As of the Closing Date, there are no outstanding share option awards or other equity incentive awards.

(b) All of the issued and outstanding Shares have been duly authorized and validly issued in compliance with the Company Governing Documents and all applicable Legal Requirements. Except as set forth in Section 3.2(b) of the Disclosure Schedule, no subscription, warrant, option, convertible security or other right (contingent or otherwise) to purchase or acquire any Shares or other capital stock of the Company is authorized or outstanding. The Company has no obligation to issue any subscription, warrant, option, convertible security or other such right or to issue or distribute to holders of any capital stock any evidence of indebtedness or assets of the Company, as the case may be. Except pursuant to the Company Governing Documents as of the date hereof, no Company has any obligation to purchase, redeem or otherwise acquire any capital stock or any interest therein or to pay any dividend or make any other distribution in respect thereof. There are no outstanding or authorized capital stock appreciation, phantom stock, profit participation or similar rights with respect to the Company.

3.3 Company Subsidiaries. The Company does not have any subsidiaries, and does not own or control, directly or indirectly, any security or similar interest in, or any interest convertible into or exchangeable or exercisable for any equity security, partnership interest, joint venture interest or similar interest in any Person.

3.4 Equity Agreements. Except as provided in this Agreement, as set forth in the Company Governing Documents, or as set forth in Section 3.4 of the Disclosure Schedule, there are no agreements, written or oral, between the Company and any holder of its securities or others, or among any holders of its securities, relating to the acquisition (including, without limitation, rights of first refusal, anti-dilution or pre-emptive rights), disposition, governance or voting of the Shares or other securities or interests of the Company.

3.5 Authority; No Conflict.

(a) The Company has all necessary requisite corporate power and authority to execute and deliver this Agreement, each Ancillary Agreement to be executed and delivered by the Company at Closing and each instrument required hereby to be executed and delivered by the Company at the Closing and to perform its obligations hereunder and thereunder and to consummate the transactions contemplated hereby and thereby. The execution, delivery and performance by the Company of this Agreement, each Ancillary Agreement to be executed and delivered by the Company at Closing and each instrument required hereby to be executed and delivered by the Company at the Closing and the consummation by the Company of the transactions contemplated hereby and thereby have been duly and validly authorized by all necessary corporate or similar action on the part of the Company; and no other actions on the part of the Company are necessary to authorize this Agreement or any instrument required hereby to be executed and delivered by the Company at the Closing or to consummate the transactions so contemplated.

(b) This Agreement has been, and each Ancillary Agreement and each instrument required hereby to be executed and delivered by the Company at the Closing will be, duly and validly executed and delivered by the Company and, assuming the due authorization, execution

and delivery by each other party or parties hereto or thereto, as applicable, constitutes or will constitute, as applicable, a legal, valid and binding obligation of the Company, enforceable against the Company in accordance with its terms, subject to bankruptcy, insolvency, fraudulent conveyance, reorganization, moratorium and other laws relating to or affecting creditors' rights generally and general equitable principles (whether considered in a proceeding in equity or at law).

(c) The execution, performance and delivery of this Agreement by the Company, each Ancillary Agreement to be executed, performed and delivered by the Company at Closing and each instrument required hereby to be executed, performed and delivered by the Company at the Closing, the compliance by the Company with the provisions of this Agreement, each Ancillary Agreement to be executed, performed and delivered by the Company at Closing and each instrument required hereby to be executed, performed and delivered by the Company at the Closing and the consummation of the transactions contemplated hereby or thereby, will not (i) conflict with or violate the Company Governing Documents, (ii) conflict with, result in a breach of, constitute (with or without due notice or lapse of time or both) a default under, result in the acceleration of, create in any party the right to accelerate, terminate, modify or cancel, or require any notice to, or result in the loss of any benefit to which the Company is entitled under, any Material Contract, Permit, Lien or other material interest to which the Company is a party or by which the Company is bound or to which its assets are subject, (iii) result in the creation or imposition of any Lien upon any assets of the Company or any Shares, or (iv) violate any Legal Requirement applicable to the Company or Sellers or any of their respective properties or assets, except in each case in respect to items in clauses (i) through (iv) of this Section 3.5(c), for any such conflicts, violations, breaches, defaults or other occurrences that would not, individually or in the aggregate, be likely to be material to the Company.

3.6 Consents; Notices. No consent, approval, order, permit or authorization of, or registration, declaration or filing with, or notification to (together, the "Consents") any Governmental Authority is required to be obtained by the Company or to the Sellers' Knowledge, Sellers or the Seller Representative, in connection with the execution and delivery of this Agreement, the Ancillary Agreements or the other transactions to be consummated as contemplated by this Agreement.

3.7 Absence of Changes. Except as set forth in Section 3.7 of the Disclosure Schedule, since December 31, 2022, (x) there has not been a Material Adverse Effect; (y) the business of the Company has been conducted in all material respects in the ordinary course of business (except as contemplated by this Agreement and taking into account any reactions to any material event or change in circumstance related to the COVID-19 virus that occurs following the date of this Agreement); and (z) there has not been:

(a) any change or event (including, without limitation, changes in the business, operations, assets (whether tangible or intangible) or liabilities (including contingent liabilities), results of operations or the conditions of the Company);

(b) any issuance of any capital stock of the Company, or any instrument exercisable or convertible into such interest, other than the Convertible Loan Agreements;

(c) any entry by the Company into any material transaction other than in the ordinary course of business or as contemplated herein or in the Ancillary Agreements;

(d) any discharge or satisfaction by the Company of any material Lien or payment by the Company of any material obligation or material liability other than in the ordinary course of business or as contemplated herein or in the Ancillary Agreements;

(e) any declaration, setting aside or payment of any dividend or other distribution with respect to, or any direct or indirect redemption or acquisition of, any of the securities of the Company;

(f) any waiver of any valuable right of the Company or cancellation of any material debt or claim held by the Company;

(g) any increase in the compensation paid or payable or employee benefits provided to any officer, member, manager, director, employee or agent of the Company other than in the ordinary course of business;

(h) any entry into or agreement to enter into a collective bargaining agreement or similar labor contract, no labor dispute involving the Company and no material change in the personnel of the Company or the terms and conditions of their employment, other than in the ordinary course of business;

(i) any material acquisition or disposition or abandonment of any assets (or any contract or arrangement therefor) except in the ordinary course of business nor any other transaction by the Company otherwise than for fair value in the ordinary course of business;

(j) any purchase, sale, assignment, transfer, license, lease, abandonment or other disposition of any Intellectual Property;

(k) any change in accounting methods or practices of the Company, except as required by applicable law;

(l) any loss, or any development that is expected by the Company to result in a loss, of any significant supplier, customer, distributor or account of the Company (other than the completion in the ordinary course of business of specific projects for customers);

(m) any amendment or termination of any material contract or agreement to which the Company is a party or by which it is bound;

(n) any mortgage, lien or other encumbrance placed on any of the properties of the Company other than in the ordinary course of business for equipment leased, consistent with past practices;

(o) any contingent liability incurred by the Company as guarantor or otherwise with respect to the obligations of others;

(p) any obligation or liability incurred by the Company to any of its managers, directors, shareholders, or employees, or any loans or advances made by the Company to any of its managers, directors, shareholders, or employees, except normal compensation and expense allowances payable to employees in the ordinary course of business;

(q) any arrangements relating to any royalty or similar payment based on the revenues, profits or sales volume of the Company, whether as part of the terms of the Company's capital stock or by any separate agreement, other than in the ordinary course of business;

(r) any liability in respect of Tax outside the ordinary course of business, any new, change in, or revocation of, any material Tax election; any settlement or compromise of any claim, notice, audit report or assessment in respect of a material amount of Taxes; any change in any annual Tax accounting period; any adoption or change of any procedures, practices or principles consistently applied in respect of (i) the determination of the profit for Tax purposes, including any depreciation schedule, and the moment revenue, income, gain, loss, costs and expenditures are recognized for Tax purposes and (ii) the valuation of the assets and liabilities for Tax purposes; any filing of a material Tax Return in a manner not consistent with applicable Tax Law or past practice; any amendment, revocation or re-submittance of any Tax Return previously submitted to a Tax Authority; any entrance into a material Tax allocation agreement, Tax sharing agreement, Tax indemnity agreement or closing agreement made relating to any Tax; any surrender of any right to claim a material Tax refund; or any consent to an extension or waiver of the statute of limitations period applicable to any Tax claim or assessment; and

(s) any commitment (contingent or otherwise) to do any of the foregoing.

3.8 Financial Statements.

(a) Attached hereto as Section 3.8(a) of the Disclosure Schedule are true, correct and complete copies of the following financial statements (collectively, the "Financial Statements"): (i) the unaudited balance sheets of the Company as of December 31, 2020 and December 31, 2021 and the related statements of operations and cash flows for the twelve (12) months then ended, and (ii) the unaudited balance sheet of the Company as of December 31, 2022 (the "Interim Balance Sheet") and the related statements of operations and cash flows for the twelve (12) months then ended (the "Interim Financial Statements"). The Financial Statements fairly present in all material respects the consolidated financial condition and the consolidated results of operations of the Company for the dates or periods indicated. The Financial Statements have been prepared in conformity with GAAP applied on a consistent basis in accordance with past practices of the Company, except, in the case of the Interim Financial Statements, for the absence of footnotes and other presentation items and for normal year-end adjustments.

(b) As of the date of this Agreement, to the Knowledge of the Sellers, the Company has no liabilities of a type required to be reflected in or reserved for on a balance sheet prepared in accordance with GAAP, except for (i) liabilities that may be reflected in or reserved for in the Financial Statements or disclosed in the notes thereto, (ii) liabilities that have arisen since the date of the Interim Balance Sheet in the ordinary course of business of the Company, (iii) liabilities incurred in connection with the transactions contemplated by this Agreement or in compliance

with the terms of this Agreement or the Ancillary Agreements, or (iv) as set forth in Section 3.8(b) of the Disclosure Schedule.

(c) All of the accounts and notes receivable of the Company, whether reflected on the Interim Financial Statements or arising since the date of the Interim Financial Statements, have arisen from bona fide transactions in the ordinary course of business consistent with past practice. All accounts payable of the Company are legal, valid, and binding obligations of the Company and arose from bona fide transactions for services in the ordinary course of business.

3.9 Taxes.

(a) The Company has duly and timely filed (taking into account any available extensions of time for such filings) all Tax Returns that it was required to file. All such Tax Returns are true, correct and complete in all material respects. All Taxes owed by the Company have been paid when due. The Company has no liabilities for unpaid Taxes that have not been accrued for or reserved on the Interim Balance Sheet, whether asserted or un-asserted, contingent or otherwise and the Sellers do not have any Knowledge of any basis for the assertion of any such liability attributable to the Company or its assets or operations.

(b) The Company is not currently the beneficiary of any extension of time to file any Tax Return. No written claim has been received from a Tax Authority in a jurisdiction in which the Company does not file Tax Returns that the Company is subject to taxation by that jurisdiction. There are no Liens on any of the Company's assets for Taxes.

(c) No deficiencies for Taxes with respect to the Company have been claimed, proposed or assessed in writing by any Tax Authority except for any deficiencies that have been satisfied by payment, settled or withdrawn. There are no pending, announced or, to the Knowledge of the Sellers, threatened Audits relating to any liabilities for Taxes of the Company. The Company has not waived any statute of limitations in respect of Taxes or agreed to any extension of time with respect to a Tax assessment or deficiency, which extension remains in effect.

(d) The Company has duly, timely and in compliance with applicable laws withheld and paid all Taxes required to have been withheld and paid in connection with amounts paid or owing to any employee, independent contractor, creditor, or securityholder of the Company or other Person.

(e) The Company is not liable for Taxes imposed on or due by any third party, including any sub-contractor, Sellers, Related Party or Affiliate of the Company, except to the extent that full provision has been made on the Interim Balance Sheet.

(f) The Company is not and has never been a member of an affiliated group of corporations filing Tax Returns on a consolidated basis or any other basis in which the profits and losses for corporate Tax purposes may be transferred among the members of the affiliated group of corporations.

(g) The Company has not (i) entered into any agreement, including advance tax rulings and advance pricing agreements, with any Tax Authority or (ii) received any decisions from any Tax Authority with respect to the Research and Development (Promotion) Act (*Wet bevordering*

speur- en ontwikkelingswerk or WBSO) or the application of the innovation box (*innovatiebox*) within the meaning of Section 2.3 of the Dutch Corporate Income Tax Act 1969 (*Wet vennootschapsbelasting 1969*).

(h) Since its inception, the Company has not claimed nor been granted exemptions from Taxes in connection with reorganizations or mergers, and there are no reorganizations or mergers in effect on or before the date of this Agreement, which will or may give rise to the assessment or payment of Taxes after the date of this Agreement.

(i) The Company has complied with applicable information reporting and has maintained and preserved directly or indirectly all records required for Tax and Subsidy purposes under any applicable Tax Laws. The Company has made complete and accurate records necessary to calculate the Tax liability or relief which would arise on a disposal or on the realization of each asset owned by the Company on the Closing Date. All records of the Company are duly kept, and are available for inspection, at the Company's premises.

(j) The Company does not own and has not agreed to acquire any asset or has agreed to enter into any transaction or has received or agreed to receive any services or facilities, including but not limited to the benefit of any license agreement, the consideration for which was or is in excess of or below the relevant market value or market price or was or is determined otherwise than on an arm's length basis. The Company is and has been in compliance in all material respects with all applicable transfer pricing laws and regulations, including the maintenance of an acceptable reasoning and adequate documentation to support any position on transfer pricing.

(k) The Company (i) is duly registered with the Tax Authority in its country of incorporation and in any other country where such registration is required for the purposes of VAT and has been so registered at all times that is has been required to be registered by VAT Legislation, (ii) is and has always been in compliance in all material respects with the VAT Legislation, (iii) has made and maintained accurate and up to date records, invoices, accounts and other documents required by or necessary for the purposes of VAT Legislation, (iv) has duly, timely and correctly made all payments and filed all returns required under VAT Legislation, (v) is entitled under VAT Legislation to deduct all of its input VAT and (vi) is not subject to any pending VAT revision periods.

(l) None of the employees of the Company is entitled to or has been entitled to in a particular year to a remuneration in excess of the amount as referred to in Article 32bb, paragraph 2, of the Dutch Payroll Tax Act (*Wet op de loonbelasting 1964*).

(m) With respect to the period up to the Closing Date, the Company only employs one (1) employee.

(n) The statutory directors who hold (a direct or indirect) substantial interest in the Company apply the wage paid-on scheme (*doorbetaaldloonregeling*) and their personal management companies take a customary wage (*gebruikelijk loon*) into account, both within the meaning of the Dutch Payroll Tax Act (*Wet op de loonbelasting 1964*).

(o) The Company has not received any analysis or advice from any of its advisers indicating that it has been a party to or otherwise involved in, any transaction, scheme or

arrangement which contains one or more of the hallmarks of Council Directive 2018/822/EU of 25 May 2018 ("DAC6") or any laws implementing DAC6 and the Company has not made any filings under DAC6. Sellers are not otherwise aware that the Company has been a party to or otherwise involved in any such transaction scheme or arrangement.

(p) The signing and consummation of the Agreement will not have any adverse Tax consequences for the Company.

(q) The Company has no liability for the material Taxes of any other Person (i) as a result of being a member of an affiliated group; (ii) as a transferee or successor, (iii) by Contract (other than Contracts entered into in the ordinary course of business and not relating primarily to Taxes), or (iv) otherwise.

(r) The Company has not been involved in any scheme, arrangement, transaction or series of transactions in which the main purposes or one of the main purposes was the avoidance, reduction, deferral or refund of Tax.

(s) The Company is not and has never been subject to Tax in any jurisdiction other than its country of incorporation, organization or formation by virtue of being treated as a resident of or having an office, employees, a permanent establishment or other place of business or taxable presence in such jurisdiction.

(t) The Company is not a party to or bound by any Tax sharing, Tax indemnity, or Tax allocation agreement, and the Company does not have any Liability to another party under any such agreement.

(u) The Company is not and has never been (i) a "surrogate foreign corporation" within the meaning of Section 7874(a)(2)(B) of the Code or (ii) treated as a "domestic corporation" under Section 7874(b) of the Code.

(v) The Company is not and has never been (i) a "controlled foreign corporation" within the meaning of Section 957(a) of the Code, (ii) a "passive foreign investment company" within the meaning of Section 1297(a) of Code, or (iii) a business entity created or organized both in the United States and in a foreign jurisdiction such that such entity would be taxable in the United States as a domestic entity pursuant to United States Treasury Regulations Section 301.7701-5(a).

(w) The Company is not a party to any joint venture, partnership or other Contract or arrangement that is treated as a partnership for U.S. federal income Tax purposes.

(x) No entity classification election for U.S. Tax purposes has ever been filed with or with respect to the Company.

3.10 Real Property.

(a) The Company does not own any real property.

(b) The Company has not and is not currently leasing or subleasing, or otherwise has not been nor is being granted rights of use or occupancy, for any real property.

3.11 Personal Property. The Company has good title to all of the material personal property and assets (whether tangible or intangible, but excluding Intellectual Property, which is the subject of Section 3.16) reflected on the Interim Balance Sheet (other than personal property and assets sold since the date of the Interim Balance Sheet) or acquired thereafter. The Company has the right to use all of such other personal property and assets in the conduct of their respective business and operations as currently conducted. None of the properties or assets owned by the Company is subject to any Lien other than Permitted Liens.

3.12 Environmental Matters. Except as set forth in Section 3.12 of the Disclosure Schedule, (a) the Company is in compliance with all applicable Environmental Laws, except for such noncompliance as would not be material to the Company; (b) the Company has not received any written notice from any Person that is in violation of, or has liability arising under, any Environmental Laws, except for any such notice that would not be material to the Company; and (c) (i) the Company has and maintains, in full force and effect, all material Permits that are required under applicable Environmental Laws to conduct their business of the Company as now being conducted, and (ii) the Company is in compliance with all such Permits, except in each case of clauses (i) and (ii), for the failure to maintain such material Permit or for such noncompliance as would not be material to the Company.

3.13 Material Contracts.

(a) Section 3.13(a) of the Disclosure Schedule sets forth, as of the date of this Agreement, a list of all the following agreements (the "Material Contracts") to which the Company is a party or to which the Company or its assets is subject (excluding any Benefit Plan):

(i) any material agreement pursuant to which the Company is paid more than $25,000;

(ii) any material agreement pursuant to which the Company pays more than $25,000;

(iii) any agreement that cannot be terminated by the Company upon ninety (90) days' notice or less without the payment of any material penalty or material termination fee;

(iv) any collective bargaining agreement or Contract with any labor union;

(v) any Contract involving the settlement of any Action to which any unpaid amounts or future obligations remain in excess of $100,000;

(vi) any Contract with a Related Party;

(vii) any indenture, mortgage, promissory note, loan agreement, guaranty or other agreement or commitment for borrowing or any pledge or security arrangement;

(viii) any agreement under which the Company has advanced or loaned any amount to any of its directors and employees (other than advances of business and similar expenses in the ordinary course);

(ix) any contract containing covenants directly or explicitly limiting in any material respect the freedom of the Company to compete in any line of business or with any Person;

(x) any contract or agreement relating to the licensing, distribution, development, manufacturer, purchase, sale or servicing of any Intellectual Property by the Company;

(xi) any contract that (i) provides for the development of any Intellectual Property by or for the Company, (ii) provides for the purchase by the Company of any Intellectual Property, (iii) includes any grant of any Intellectual Property License or title in, to or under any Intellectual Property by the Company to any Person (other than reseller, supplier or distributor contracts entered into in the ordinary course of business) or (iv) includes any grant of any Intellectual Property License or title in, to or under any Intellectual Property by any Person to the Company that is material to the conduct or operation of the Company's business (other than non-exclusive licenses for software that is licensed under "shrink-wrap," "click-through" or other similar contracts and is generally commercially available; software as a service, cloud or similar agreements entered into in the ordinary course of business and involving payments or fees of less than $10,000 per annum; and invention assignment agreements with employees, consultants and contractors of the Company);

(xii) any employment, consulting or other service agreements with present or former members, managers, directors, employees, consultants, shareholders of the Company or any other service provider of the Company that includes any change of control payments, severance, termination or retention obligations or similar accounts payable by the Company or its Affiliates in connection with the transactions contemplated by this Agreement;

(xiii) any redemption or purchase agreements or other agreements affecting or relating to the capital stock of the Company, including, without limitation, any agreement with any shareholder of the Company which includes anti-dilution rights, registration rights, voting arrangements, operating covenants or similar provisions;

(xiv) any royalty, dividend or similar arrangement based on the revenues or profits of the Company or any contract or agreement involving fixed price or fixed volume arrangements;

(xv) any joint venture, franchise, partnership or supply agreement;

(xvi) any acquisition, merger or similar agreement;

(xvii) any contract with any governmental entity; and

(xviii) any other material contract not executed in the ordinary course of business.

(b) Except as disclosed in Section 3.13(b) of the Disclosure Schedule, each of the Material Contracts (i) is in full force and effect, (ii) represents a legal, valid and binding obligation of the Company, (iii) to the Sellers' Knowledge, represents the legal, valid and binding obligations of the other parties thereto, and (iv) is legally enforceable in accordance with its respective terms, subject to bankruptcy, insolvency, fraudulent conveyance, reorganization, moratorium and other laws relating to or affecting creditors' rights generally and general equitable principles (whether considered in a proceeding in equity or at law). The Company has not received any written notice or threat to terminate any Material Contract. Except as disclosed in Section 3.13(b) of the Disclosure Schedule, (x) each Material Contract will continue to be valid, existing and in full force and effect on identical terms immediately following the consummation of the transactions contemplated hereby, (y) the Company is not in material breach or default under such Material Contract (as applicable), and (z) to the Sellers' Knowledge, no other party to such Material Contract is in material breach or default under such Material Contract (as applicable).

3.14 Suppliers. Section 3.14 of the Disclosure Schedule sets forth, as of the date of this Agreement, a list of the Company's top ten (10) vendors and suppliers for the fiscal year ended December 31, 2021 and December 31, 2022, determined on a consolidated basis by aggregate expenditure on the products or services purchased from such vendors and suppliers (the "Material Suppliers"). The Company has not received any written notice from any such Material Supplier to the effect that any such Material Supplier is terminating its business relationship with the Company or will materially reduce its provision of products and services to the Company (whether as a result of the consummation of the transactions contemplated hereby or otherwise); provided that the foregoing shall not include the expected completion of any project or provision of products or services in the ordinary course of business.

3.15 Certain Relationships and Related Transactions. Except as provided in Section 3.15 of the Disclosure Schedule, the Company has not advanced or loaned money to any Related Party (other than expense advancements in the ordinary course of business) and the Company is not a party to any agreement with, or involving the making of any payment or transfer of assets to, any Related Party. No Sellers, and no Related Party or Affiliate of the Company (nor, to the Sellers' Knowledge, any parent, sibling, child, grandchild, or spouse of any of such Persons, or any trust, partnership, corporation or other entity or vehicle in which any of such Persons has or has had a financial interest), has, directly or indirectly (a) a material financial interest in any Person that furnished or sold (or furnishes or sells), services or products that the Company furnishes or sells (or proposes to furnish or sell), (b) a material financial interest in any Person that purchases from, or sells or furnishes to, the Company any products or services, or (c) a beneficial interest in any Material Contract.

3.16 Intellectual Property.

(a) Section 3.16(a) of the Disclosure Schedule sets forth, as of the date of this Agreement, (i) all of the issued patents and applications ("Registered Company Patents"), and trademark registrations, copyright registrations and domain name registrations owned by any of the Company, and all applications for any of the foregoing ("Registered Company Intellectual Property"), including (A) the owner, (B) the jurisdiction where issued, registered, legally

sanctioned, filed or the equivalent and (C) the particulars of any registrations or issuances including relevant filing and issuance dates, application numbers and the status thereof, and (ii) all material unregistered or common law trademarks owned or used by the Company. All Registered Company Intellectual Property is currently in material compliance with all formal Legal Requirements. All Registered Company Intellectual Property that is issued or registered and, to the Knowledge of the Sellers, any pending applications included in the Registered Company Intellectual Property is valid, subsisting, and enforceable, and has been applied for or registered in the name of the Company. The Company has made all necessary filings and paid all necessary fees due to be made or paid as of the date of this Agreement to maintain all Registered Company Intellectual Property. There are no actions that must be taken by the Company within sixty (60) days following the Closing Date, including the payment of any registration, maintenance or renewal fees or the filing of any documents, applications or articles, for the purposes of maintaining, perfecting, preserving or renewing any Registered Company Intellectual Property.

(b) The Company owns, free and clear of all Liens other than Permitted Liens, or have the right to use all material Intellectual Property used in the operation of the business of the Company as it is currently conducted, except as would not have a Material Adverse Effect and the Company has not sold, transferred, assigned or otherwise disposed of any rights or interests therein or thereto (other than non-exclusive customer license agreements). The Company has the right to bring actions for infringement of all such Intellectual Property, free and clear of any prior lien or encumbrance. The Intellectual Property owned by the Company includes all Intellectual Property necessary and sufficient for, or material to, the operation or conduct of the Company as currently conducted.

(c) Except as otherwise set forth on Section 3.16(c) of the Disclosure Schedule, to the Sellers' Knowledge, since January 1, 2021, there has not been (i) any infringement, misappropriation, or violation of any Intellectual Property right of any other Person by the Company or the operation of the business of the Company; (ii) any challenge, interference, opposition or cancellation with respect to the inventorship, ownership, validity, enforceability, registration, or use of any of the Intellectual Property rights owned the Company; (iii) any Action pending regarding infringement of any Intellectual Property owned by the Company; or (iv) any claim, or basis for any claim, relating to any of the foregoing provisions in this Section 3.16(c).

(d) Except as otherwise set forth in Section 3.16(d) of the Disclosure Schedule, to the Sellers' Knowledge, since January 1, 2021, there has not been (i) any infringement, misappropriation, or violation of any Intellectual Property owned by the Company by any Person; (ii) any challenge, interference, opposition or cancellation by the Company with respect to the inventorship, ownership, validity, enforceability, registration, or use of any of the Intellectual Property rights of any other Person; (iii) any Action pending against the Company charging the Company with infringement of any Intellectual Property right of any other Person; or (iv) any claim, or basis for any claim, relating to any of the foregoing provisions in this Section 3.16(d).

(e) Section 3.16(e) of the Disclosure Schedule sets forth, as of the date of this Agreement, a complete and accurate copy of all material Contracts relating to (i) use by any third party of material Intellectual Property owned by the Company, excluding confidentiality or non-disclosure agreements, agreements with employees or contractors, customer agreements entered into in the ordinary course of business and incidental trademark licenses or ancillary licenses to

Intellectual Property owned by the Company that are necessary to be granted to receive the benefit of services from third party service providers or (ii) the use by the Company of any material Intellectual Property in connection with the business of the Company pursuant to a license or sublicense agreement from any other Person, excluding licenses to commercially available technology and services including "shrink-wrap," "click-through" or "off-the-shelf" software and software-as-a-service licenses, other software licenses with total or annual fee payments of less than $100,000, and confidentiality or non-disclosure agreements. Except as set forth on Section 3.16(e) of the Disclosure Schedule, (i) the Company has not granted any licenses or covenants not to sue in respect of the Registered Company Intellectual Property to any Person, or entered into any distribution or marketing arrangements with respect to any of the Product each case that is in effect as of the date hereof; (ii) the Company is not, nor to the Sellers' Knowledge, any other Person, is party to any Contracts with any Person that materially limit or restrict use of the Registered Company Intellectual Property or require any payments for their use; (iii) no other Person has any joint ownership or royalty interest in the Registered Company Intellectual Property; and (iv) the Company has not entered into any Contracts (A) granting any Person the right to bring infringement actions with respect to, or otherwise to enforce rights with respect to, any of the Registered Company Intellectual Property, (B) expressly agreeing to indemnify any Person against any charge of infringement of any of the Registered Company Intellectual Property, or (C) granting any Person the right to control the prosecution or enforcement of any of the Registered Company Intellectual Property. Neither the Company nor, to the Sellers' Knowledge, any other Person is in material default under any such Contract. The Company has not sent or received any notice of termination of any such Contracts, or any similar communication or correspondence regarding the possibility of an early termination of any such Contract. There is no outstanding or threatened dispute or disagreement with respect to any such Contract, nor to the Sellers' Knowledge has the Company nor the other party thereto or any sublicensee thereof, materially breached any of its obligations under any such Contract, and all rights and obligations of the Company thereunder are valid, enforceable, and in full force and effect, and to the Sellers' Knowledge, all rights and obligations of the relevant counterparties thereunder are valid, enforceable, and in full force and effect. Each such Contract is fully transferable to Buyer and shall be exercisable by Buyer on and immediately after the Closing to the same extent as by the Company, as applicable, prior to the Closing. All milestones and other conditions set forth in any such Contract that have been required to be satisfied in order for the Company to retain any rights granted under such Contract have been timely satisfied. Except as set forth on Section 3.16(e) of the Disclosure Schedule, the Company is not bound by, and no material Intellectual Property used in connection with the business of the Company is subject to, any Contract containing any covenant or other provision that in any way limits or restricts the ability of the Company to use, exploit, assert, or enforce any such Intellectual Property anywhere in the world. Except as set forth on Section 3.16(e) of the Disclosure Schedule, no licensing fees, royalties, profit participations, or other payments are due or payable by the Company in connection with the Product or any Registered Company Intellectual Property.

(f) To the Sellers' Knowledge, the conduct of the business of the Company as currently conducted by the Company does not infringe or misappropriate any Intellectual Property, including any issued patent, registered trademark, registered copyright or registered Internet domain name or trade secret, of a third party, except as would not have a Material Adverse Effect. To the Sellers' Knowledge, none of the Intellectual Property owned by the Company is being infringed or misappropriated by any other Person.

(g) The Company has, and enforces, a policy requiring each employee, consultant and contractor to execute proprietary information, confidentiality and assignment agreements and all current and former employees, consultants and contractors of the Company who is or was involved in the creation of any material Intellectual Property owned by the Company have properly executed such an agreement in substantially such form, and, to the Knowledge of the Sellers, no trade secrets, source code or other confidential Intellectual Property of the Company has been disclosed by the Company to any Person except pursuant to valid and appropriately protective non-disclosure, assignment and/or license agreements. Each employee, consultant and contractor employed by the Company who is or was involved in the creation of any Intellectual Property owned by the Company has assigned to one of the Company all of such employee, consultant or contractor's right, title and interest in or to such Intellectual Property (or all such rights vested in the Company by operation of Law).

(h) All Intellectual Property owned by the Company will be owned or available for use by the Company immediately subsequent to the Closing Date on substantially identical terms and conditions as owned or used by the Company immediately prior to the Closing Date. The transactions contemplated hereby will not adversely affect the validity or enforceability of the Intellectual Property owned by the Company under applicable laws and will not result in the loss of use of, or the loss of the right, to any material Intellectual Property owned by the Company.

(i) The Company is not a party to or otherwise bound by any settlement agreement that could reasonably be expected, individually or in the aggregate, to materially and adversely affect the Company's rights to use any Intellectual Property owned by the Company in the operation or conduct of the business as currently conducted by the Company.

(j) The Company has taken reasonable security measures to protect the secrecy, confidentiality and value of all Intellectual Property, including trade secrets, owned by the Company.

(k) Except as set forth on Schedule 3.16(k) of the Disclosure Schedule, no (i) government funding, including funding pursuant to a government grant; (ii) facilities or personnel of a university, college, other educational or medical institution or research center; or (iii) funding from any Person was used in the development of the Intellectual Property owned by the Company. To the Sellers' Knowledge, no current or former employee, consultant, independent contractor, or agent of the Company, who was involved in, or who contributed to, the creation or development of any Intellectual Property, was employed by or has performed services for any government, university, college or other educational or medical institution or research center during a period of time during which such employee, consultant, independent contractor, or agent was also performing services for the Company.

3.17 Data Privacy. In connection with the Company's collection, storage, use and/or disclosure of any information that constitutes "personal information," "personal data" or "personally identifiable information" as defined in applicable laws (collectively "Personal Information"), the Company is, and for the last three (3) years has been, to the Sellers' Knowledge, in material compliance with all applicable laws pertaining to data privacy, data protection or data transfer ("Privacy Laws"). The Company maintains and has maintained for the last three (3) years commercially reasonable physical, technical, and administrative security measures and policies

designed to protect all Personal Information in the Company's possession from and against unlawful, accidental or unauthorized access, destruction, loss, use, modification or disclosure.

3.18 Personnel.

(a) The Company is in compliance in all material respects with all Legal Requirements relating to labor and employment, including all such Legal Requirements relating to wages, hours, plant closings, collective bargaining, discrimination, safety and health, and immigration.

(b) The Company is not subject to any collective bargaining agreement or any other Contract with a labor union and no employee of the Company is represented by a labor union. There are no material labor disputes currently pending or filed within the last three (3) years under any formal grievance procedure, arbitration or litigation. There is not pending nor has there been in the last three (3) years, to the Sellers' Knowledge, threatened, any material labor strike, slowdown, lockout, work stoppage or other material labor dispute involving employees of the Company, and, to the Sellers' Knowledge, no union organizing activities are taking place or have taken place with respect to such employees.

(c) No employee of the Company is currently on sick leave or has been so for more than 6 weeks during the past 12 (twelve) months.

(d) The transactions contemplated by this Agreement will not will increase or accelerate any obligations deriving from any applicable bonus, profit sharing, savings, redundancy or exit arrangements, share option or stock appreciation rights schemes or share repurchase schemes or any similar arrangements in existence for towards or for the benefit of any current or former employee, any current or former director or any current or former contractor of the Company.

(e) All holidays the employees of the Company are entitled to in respect of the period up to the Closing Date have either been used, compensated or have been adequately provided for in the accounts of the Company.

(f) No works council or other employee representative body is installed at the level of the Company, nor is the Company obliged to install such employee participation body on the basis of the Dutch Works Councils Act.

(g) All pension arrangements of the Company (the "Pension Arrangements") have been provided to the Buyer by the Sellers. The Pension Arrangements apply to all current and former employees and current and former directors of the Company and the Company is not a party to any other pension arrangement relating to any current or former employees or current or former directors, including pension insurance or excess (excedent) insurance, other than the Pension Arrangements.

(h) All premiums that have fallen due in respect of the Pension Arrangements for the period up to and including the Closing Date have either been paid or are adequately provided for in the accounts of the Company. As per the Closing Date, the Company does not have any obligation with respect to Pension Arrangements, whether or not conditional or contingent,

including but not limited to back-service obligations, which are not fully funded or adequately provided for in their accounts.

3.19 Insurance. All material insurance policies with respect to the properties, assets or business of the Company, which (other than policies maintained in connection with Benefit Plans) are set forth on Section 3.19 of the Disclosure Schedule, are in full force and effect and all premiums due and payable thereon have been paid in full as of the date of this Agreement. As of the date of this Agreement, the Company has not received written notice threatening cancellation or non-renewal of, or a material premium increase with respect to, any such insurance policy. The Company is not in material default with respect to any provision contained in any insurance policy or has failed to give any material notice or present any material claim under any insurance policy in due and timely fashion. For the last three (3) years, the Company has not (i) had an insurance claim with respect to an amount in excess of $100,000 rejected or payment with respect thereto denied by its insurance provider for such claim, (ii) had an insurance claim in which there is an outstanding reservation of rights or (iii) had the policy limit under any insurance policy exhausted or materially reduced.

3.20 Litigation. Except as set forth in Section 3.20 of the Disclosure Schedule, as of the date of this Agreement, no Action is pending or, to the Sellers' Knowledge, threatened in writing, against (i) the Company, (ii) the Company's assets or properties or (iii) to the Sellers' Knowledge, against any officer, director or key employee of the Company in their respective capacities in such positions. As of the date of this Agreement, there are no outstanding orders, awards, judgments, injunctions or decrees of any Person against the Company or the Company's assets or properties.

3.21 Compliance with Laws; Permits.

(a) The Company has complied in all material respects with, and is operating in compliance in all material respects with, all Legal Requirements applicable to its business. Except as set forth in Section 3.21 of the Disclosure Schedule, since its inception, the Company has not been alleged to have violated or been charged with any violation of any provision of any federal, state or local law or administrative regulation in respect of its business. The Company has not entered into or been subject to any judgment, consent decree, compliance order or administrative order with respect to any aspect of the business, affairs, properties or assets of the Company or received any request for information, notice, demand letter, administrative inquiry or formal or informal complaint or claim from any regulatory agency with respect to any aspect of the business, affairs, properties or assets of the Company.

(b) The Company has and has held all material Permits necessary to be had by it to conduct its business. As of the date hereof, no suspension or cancellation of any such Permits is pending or, to the Sellers' Knowledge, threatened and the Company is not in material violation of or in material default under any Permit. To the Sellers' Knowledge, there is no (a) present or ongoing investigation, review or proceeding by any Person that could reasonably be expected to result in a claim or notice of violation or non-compliance with, or a revocation, non-renewal or a material modification of, any such Permit in any material respect, or (b) event, omission or condition that could reasonably be expected to result in a notice of violation or non-compliance with, or a revocation, non-renewal or material modification or revision of, any such Permit in any material respect.

3.22 FDA and Healthcare Regulatory Compliance .

(a) The Company has operated and currently is in compliance in all material respects with applicable Legal Requirements, including Health Care Laws. The Company has not received notice of any pending or threatened claim, suit, proceeding, hearing, enforcement, audit, investigation, arbitration or other action, including any Warning Letters, untitled letters, or similar correspondence, from the FDA or any other Governmental Authority administering Health Care Laws (collectively, "Regulatory Authorities") alleging that any operation or activity the Company is in violation of any applicable Legal Requirements, including any Health Care Laws, in any material respect.

(b) The Company holds, has held, is operating, and has operated in material compliance with such Permits of the FDA and other Regulatory Authorities required for the conduct of its business (collectively, the "Regulatory Permits"), and all such Regulatory Permits are valid and in full force and effect. The Company has fulfilled and performed all of its material obligations with respect to the Regulatory Permits, and no event has occurred which allows, or after notice or lapse of time would allow, revocation or termination thereof or results in any other material impairment of the rights of the holder of any Regulatory Permit.

(c) The Company has not conducted or initiated any clinical studies or clinical trials. The pre-clinical and other studies and tests conducted by or on behalf of or sponsored by the Company or in which the Company or its product candidates have participated were and, if still pending, are being conducted in all material respect in accordance with standard medical and scientific research procedures and all applicable Legal Requirements, including, but not limited to, the Federal Food, Drug and Cosmetic Act and its applicable implementing regulations, including 21 C.F.R. Part 58. The Company has not submitted any investigational new drug application to the FDA or any similar request or application for a Regulatory Permit to conduct clinical studies or clinical trials to another Regulatory Authority.

(d) The Company has filed, maintained or submitted all material reports, documents, forms, notices, applications, records, claims, submissions and supplements or amendments as required by any Health Care Laws, and all such reports, documents, forms, notices, applications, records, claims, submissions and supplements or amendments were complete and accurate on the date filed in all material respects (or were corrected or supplemented by a subsequent submission). The Company is not a party to any corporate integrity agreements, deferred or non-prosecution agreements, monitoring agreements, consent decrees, settlement orders, or similar agreements with or imposed by any Governmental Authority. Additionally, neither the Company nor any of its employees, directors, or, to the Knowledge of the Sellers, agents has been excluded, suspended or debarred from participation in any U.S. federal health care program or human clinical research or, to the Knowledge of the Sellers, is subject to a governmental inquiry, investigation, proceeding, or other similar action that could reasonably be expected to result in debarment, suspension, or exclusion.

3.23 Foreign Corrupt Practices. The Company has complied in all material respects with (i) applicable laws governing the importation or exportation of products or merchandise and (ii) any other laws regarding the use of funds for political activity or commercial bribery. Neither the Company nor any director, employee or agent of the Company have, at any time, (i) made or

caused to be made or provided, directly or indirectly, any type of payment, gift, contribution or similar item to (A) a governmental official, political party, or candidate for office for the purpose of influencing a decision, inducing an official to violate their lawful duty, securing an improper advantage, or inducing an official to use their influence to affect a governmental decision, or (B) any of its customers, distributors and/or suppliers or their respective directors, officers, agents or employees, other than payments required under written contracts between the Company and its customers, distributors and/or vendors, or (ii) accepted or received any unlawful payments, gifts, contributions or similar items.

3.24 Brokers and Finders. The Company has not retained, utilized or been represented by any broker or finder in connection with the transactions contemplated by this Agreement.

3.25 Disclosure. This Agreement (including the Schedules hereto) does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements contained herein or therein not misleading in light of the circumstances under which they were made. No representation or warranty by the Company contained in this Agreement, and no statement contained in any Schedule (including any supplement or amendment thereto) relating to such representations or warranties, and the other documents to be delivered at the Closing by or on behalf of the Company in connection with the transactions contemplated hereby, contains or will contain any untrue statement of material fact or omits or will omit to state a material fact necessary in order to make the statements and information contained therein true. All information supplied by the Sellers and their agents and advisers to the Buyer or its agents and advisers is true and accurate and not misleading and the Sellers and their agents and advisers have made available to the Buyer or its agents and advisers true, correct and complete copies of all documents described on any Schedule hereto.

Section 4.
REPRESENTATIONS AND WARRANTIES REGARDING SELLERS

Each Seller represents and warrants to Buyer, as of the date of this Agreement (unless the particular statement speaks expressly as of another date, in which case it is true, complete and correct as of such other date), subject, in each case, to the exceptions provided in the Disclosure Schedule, as follows:

4.1 Right to Sell Shares; Binding Effect; Organization and Power. Each Seller has all requisite power and full legal right to enter into this Agreement and each Ancillary Agreement to which each Seller is to be a party, to perform all of such Seller's agreements and obligations hereunder or thereunder in accordance with its terms, and to sell to Buyer all of the Shares owned by such Seller. This Agreement has been, and each Ancillary Agreement to which each Seller will be a party will be, duly executed and delivered by each Seller, assuming the due authorization, execution and delivery by the other parties hereto and thereto (other than the Sellers) and constitutes or will constitute, as applicable, the legal, valid and binding obligation of Sellers, enforceable against Sellers in accordance with its terms, except as such enforceability may be subject to applicable bankruptcy, reorganization, insolvency, moratorium and similar laws affecting the enforcement of creditors' rights generally and by general principles of equity. Each Seller is duly organized, validly existing and in jurisdictions where that is a relevant concept, in

good standing under the laws of its jurisdiction of formation, and each Seller's organizational documents (of which such Seller is not in material violation) are in full force and effect.

4.2 Title to Interests, Liens, etc.. Each Seller has record and beneficial ownership of the Shares, free and clear of any Lien (other than restrictions that may, following the Closing, be applicable on any subsequent transfer by Buyer under applicable securities laws or the Company Governing Documents), and the Shares held by the Sellers constitute all of the capital stock in the Company owned beneficially or held of record by the Sellers as of the date of this Agreement. Upon the consummation of the transactions contemplated hereby, Buyer will acquire record and beneficial ownership of all of the Shares held by Sellers, free and clear of any Lien (other than restrictions that may, following the Closing, be applicable on any subsequent transfer by Buyer under applicable securities laws or the Company Governing Documents). Except as set forth in Section 4.2 of the Disclosure Schedule, Sellers do not own any other securities of the Company of any class or kind, including any debt securities of any class or kind, nor do the Sellers have any right or option to subscribe for, or to purchase, shares or other equity securities or debt securities of the Company. Except as provided in this Agreement, any Ancillary Agreement or the Company Governing Documents, as applicable, each Seller is not party to or bound by any agreement or instrument affecting or relating to such Seller's right to transfer or vote the Shares owned by such Seller.

4.3 No Conflicts. The execution, performance and delivery of this Agreement and the other Ancillary Agreements to which each Seller is a party by such Seller and each other instrument required hereby to be executed, performed and delivered by each Seller at the Closing pursuant to this Agreement or the Ancillary Agreements, the compliance by each Seller with the provisions of this Agreement, the Ancillary Agreements to which each Seller is a party and each instrument required hereby to be executed, performed and delivered by each Seller at the Closing and the consummation of the transactions contemplated hereby or thereby, will not materially conflict with, result in a breach of, constitute (with or without due notice or lapse of time or both) a default under, result in the acceleration of, create in any party the right to accelerate, terminate, modify or cancel, or require any notice to, or result in the loss of any material benefit to which each Seller is entitled under any Contract, Permit, Lien or other interest to which such Seller is a party or by which such Seller is bound or to which its assets are subject, or violate any Legal Requirement applicable to each Seller or any of such Seller's properties or assets in any material respect.

4.4 Governmental Consents. No consent, approval or authorization of, or registration, qualification or filing with, any Governmental Authority is required for the execution, performance and delivery of this Agreement or any Ancillary Agreement to which each Seller is to be a party by each such Seller or for the consummation by each Seller of the transactions contemplated hereby and thereby.

4.5 Litigation. No Action is pending or, to the knowledge of each Seller, threatened, against each such Seller with respect to such Seller's execution, performance and delivery of this Agreement or any Ancillary Agreement to which each Seller is to be a party or the consummation by each Seller of the transactions contemplated hereby or thereby. No Action is pending or, to the knowledge of each Seller, threatened against each such Seller before any arbitrator or court or other Governmental Authority which (a) if adversely determined, would be reasonably likely to result in payments, penalties or fines payable by the Company, or (b) challenges the validity of

this Agreement or any Ancillary Agreement or any action taken or to be taken in connection herewith or therewith.

Section 5.
REPRESENTATIONS AND WARRANTIES REGARDING BUYER

Buyer represents and warrants to the Company and Sellers, as of the date of this Agreement (unless the particular statement speaks expressly as of another date, in which case it is true, complete and correct as of such other date) as follows:

5.1 Organization and Standing. Buyer (a) is duly organized and validly existing under the laws of the jurisdiction of its incorporation, (b) has all requisite power and authority to carry on its business as it is now being conducted in all material respects, and (c) is duly qualified to do business in each of the jurisdictions in which the ownership, operation or leasing of its properties and assets and the conduct of its business requires it to be so qualified, licensed or authorized, except for those jurisdictions where the failure to be so qualified, licensed or authorized would not reasonably be expected to have a Material Adverse Effect on Buyer or materially impair the ability of Buyer to consummate the transactions contemplated by this Agreement.

5.2 Authority for Agreement; No Conflict. (a) Buyer has all necessary corporate or similar power and authority to execute and deliver this Agreement, each Ancillary Agreement, and each instrument required hereby or thereby to be executed and delivered by Buyer at the Closing, and to perform its obligations hereunder and thereunder and to consummate the transactions contemplated hereby and thereby. The execution, delivery and performance by Buyer of this Agreement, each Ancillary Agreement, and each instrument required hereby or thereby to be executed and delivered by Buyer at the Closing and the consummation by Buyer of the transactions contemplated hereby and thereby have been duly and validly authorized by all necessary corporate action, and no other corporate or similar proceedings on the part of Buyer are necessary to authorize this Agreement, each Ancillary Agreement or to consummate the transactions so contemplated.

(b) This Agreement and the Ancillary Agreements have been and each instrument required hereby or thereby to be delivered by Buyer at the Closing will be duly and validly executed and delivered by Buyer, and, assuming the due authorization, execution and delivery by the other parties hereto or thereto, constitutes or will constitute a legal, valid and binding obligation of Buyer, as the case may be, enforceable against Buyer in accordance with its terms, subject to bankruptcy, insolvency, reorganization or similar laws of general application affecting the rights and remedies of creditors, and to general equity principles.

(c) Buyer’s execution and delivery of this Agreement, each Ancillary Agreement, and each instrument required hereby to be executed and delivered by Buyer at the Closing, and the compliance with the provisions of this Agreement and each Ancillary Agreement by Buyer and the consummation by Buyer of the transactions contemplated hereby or thereby, will not (i) conflict with or violate the organizational documents of Buyer, each as amended to date and currently in effect, (ii) violate any Legal Requirement applicable to Buyer or any of its properties or assets or (iii) result in a material breach of, or constitute a material default (or event which with the giving of notice or lapse of time, or both, would become a material default) under, or give rise

to a right of termination, cancellation or acceleration of any obligation or to loss of a benefit under, or result in the creation of any Lien (not including Permitted Liens) upon any of the properties, rights or assets of Buyer pursuant to, any Contract to which Buyer is a party or by which it is bound or affected, except in the case of clauses (ii) and (iii) above, any such conflicts, violations, defaults, rights or Liens that would not reasonably be expected to prevent, delay, or materially impair the ability of Buyer to consummate the transactions contemplated by this Agreement.

(d) No consent of, or registration, declaration, notice or filing with, any Governmental Authority is required to be obtained or made by, or given to, Buyer in connection with the execution, delivery and performance of this Agreement or the consummation of the transactions contemplated hereby, other than (i) such consents, approvals, orders authorizations, registrations, declarations, notices and filings as may be required under applicable state and federal securities laws and the securities laws of any foreign country, and (ii) where the failure to obtain such consent or to make such registration, declaration, notice or filing would not when taken together with all other such failures by Buyer reasonably be expected to prevent, delay or materially impair the ability of Buyer to consummate the transactions contemplated by this Agreement.

5.3 Brokers and Finders. Neither Buyer nor any of its Affiliates have retained, utilized or been represented by, or have any liability or obligation to pay fees or commissions to, any broker, finder or agent in connection with the transactions contemplated by this Agreement.

5.4 Litigation. As of the date of this Agreement, no Action is pending or, to the Buyer's Knowledge, threatened against the Buyer before any arbitrator or court or other Governmental Authority which (i) challenges the validity of this Agreement or any Ancillary Agreement or any action taken or to be taken in connection herewith or therewith, or (ii) would, individually or in the aggregate, reasonably be expected to prevent, delay or materially impair Buyer's ability to perform its obligations hereunder or to consummate the transactions contemplated hereby.

5.5 Investment. Buyer is acquiring the Shares for its own account as an investment without the present intent to sell, transfer or otherwise distribute Shares to any other Person. Buyer has made, independently and without reliance on any of Company or Sellers (except to the extent that Buyer has relied on the representations and warranties set forth in this Agreement, the Ancillary Agreements and in any document, certificate or other instrument required to be delivered to Buyer under this Agreement), its own analysis of the Shares and the Company. Buyer acknowledges that the Shares are not registered pursuant to the Securities Act and that none of the Shares may be transferred, except pursuant to an applicable exception under the Securities Act.

5.6 Financing. Buyer has the funds necessary to (x) make the payments required hereunder, (y) pay all fees and expenses to be paid by Buyer in connection with the transactions contemplated by this Agreement and (z) satisfy all other payment obligations at the Closing that

may arise in connection with, or may be required in order to consummate, the transactions contemplated by this Agreement.

Section 6.
ADDITIONAL AGREEMENTS

6.1 Confidentiality; Books and Records. Each of the Buyer, the Company and Sellers agree to be bound by and comply with the terms and provisions of that certain letter agreement dated October 3, 2022 by and between Rhythm Pharmaceuticals, Inc. and Xinvento B.V. (the "Confidentiality Agreement"), as if each of the Buyer, the Company and Sellers were an original party to such agreement. The Confidentiality Agreement is hereby incorporated in this Agreement by reference and made a part of this Agreement and will survive the execution of this Agreement notwithstanding the terms thereof. If a conflict arises between the provisions of this Agreement and the provisions of the Confidentiality Agreement, then the provisions of the Confidentiality Agreement will control.

6.2 Public Disclosure. From and after the Closing Date, Sellers and the Seller Representative shall not issue a press release or any other public disclosures concerning the transactions contemplated hereby, without the written approval of Buyer which shall not be unreasonably withheld, conditioned or delayed.

6.3 Cooperation; Further Actions. Following the Closing, the parties hereto shall use all reasonable efforts to take or cause to be taken all actions, execute and deliver such additional instruments, documents, conveyances or assurances and to do or cause to be done all other things, necessary, proper or advisable, or otherwise reasonably requested by another party hereto, in order for such party to fulfill and perform his, her or its obligations in respect of this Agreement and the Ancillary Agreements to which such Person is a party, or otherwise to consummate and make effective the transactions contemplated hereby and thereby and carry out the intent and purposes of this Agreement (which include the transfer to Buyer of the entire ownership of the Company and intended related benefits of the business of the Company).

6.4 Seller Release of the Company and Buyer.

(a) As a material inducement to Buyer's willingness to enter into and perform this Agreement and to purchase the Shares pursuant to the terms of this Agreement for the consideration to be paid or provided to the Sellers in connection with such purchase, each Seller, on behalf of itself and each of its Affiliates and Representatives, hereby releases and forever discharges Buyer, the Company and each of their individual, joint or mutual, past, present and future directors, officers (to the extent applicable), employees, representatives, affiliates, shareholders, controlling Persons, subsidiaries, successors and assigns (individually, a "Releasee" and collectively, "Releasees") from any and all actions, orders, obligations, contracts, agreements, debts and liabilities whatsoever, whether known or unknown, suspected or unsuspected, both at law and in equity, which each Seller or any of its respective Representatives now has, have ever had or may hereafter have against the respective Releasees arising contemporaneously with or prior to the Closing or on account of or arising out of any matter, cause or event occurring contemporaneously with or prior to the Closing, including, but not limited to, any rights to indemnification or reimbursement from the Company, whether pursuant to its respective Company

Governing Document, contract or otherwise and whether or not relating to claims pending on, or asserted after, the Closing; provided, however, that (i) nothing contained herein shall operate to release any obligation of Buyer arising under this Agreement and the other Ancillary Agreements, and (ii) this release set forth in this Section 6.4 shall not release ordinary course payroll payments due to any Seller who is an employee of the Releasees.

(b) Each Seller hereby irrevocably covenants to refrain from, directly or indirectly, asserting any claim or demand, or commencing, instituting or causing to be commenced, any proceeding of any kind against any Releasee, based upon any matter purported to be released hereby.

(c) Without in any way limiting any of the rights and remedies otherwise available to any Releasee, each Seller shall indemnify and hold harmless each Releasee from and against all loss, liability, claim, damage (including incidental and consequential damages) or expense (including costs of investigation and defense and reasonable attorney's fees) whether or not involving third party claims, arising directly or indirectly from or in connection with the assertion by or on behalf of such Seller of any claim or other matter purported to be released pursuant to this Section 6.4.

(d) In the event that any provision of this Section 6.4 is held invalid or unenforceable by any court of competent jurisdiction, the other provisions of this Section 6.4 will remain in full force and effect. Any provision of this Section 6.4 held invalid or unenforceable only in part or degree will remain in full force and effect to the extent not held invalid or unenforceable.

6.5 Joint Steering Committee.

(a) Effective as of the Closing, the Company shall establish a joint steering committee (the "Joint Steering Committee") that shall initially be composed of (i) David Meeker, MD, for so long as he is Chief Executive Officer of Rhythm Pharmaceuticals, Inc., and (ii) a representative of the Sellers, initially being Claudine van der Sande (each, a "JSC Member"). The Joint Steering Committee shall have the limited authority to make any decision (the "Discontinuation Decision") to discontinue the development of all compounds targeting SUR1/Kir6.2 for the lead indications of CHI (the "Development") until such product is granted market approval in the United States and the European Union; provided, that, the Joint Steering Committee shall have no other authority, rights, obligations, duties or otherwise except for the Discontinuation Decision and, for the avoidance of doubt, the Joint Steering Committee shall have no authority in identifying the Lead Candidate or Second Molecule or making any programmatic decisions with respect to any compounds.

(b) All decisions by the Joint Steering Committee will be made by consensus, with one vote cast by each JSC Member. The JSC Members shall attempt in good faith to resolve any disputes and, if the JSC Members are unable to come to a consensus after ten (10) Business Days, the Joint Steering Committee shall refer the dispute to a disinterested individual, who has appropriate scientific, technical and regulatory expertise (as relevant) to resolve any such disputes referred to him or her under this Agreement (an "Independent Member"), who is mutually agreed to by both of the JSC Members. If the JSC Members cannot agree on a mutually acceptable Independent Member within thirty (30) days after either party has determined that the parties

cannot reach agreement with respect to a dispute, then within five (5) Business Days after the expiration of such thirty (30) day period, each of the JSC Members shall appoint one Independent Member who shall jointly select a third Independent Member within five (5) Business Days after the last to occur of their respective appointments to arbitrate the referred matter. The Independent Member mutually agreed by the JSC Members or, if such parties cannot agree, the third Independent Member selected by the party-appointed Independent Members is referred to as the "Selected Independent Member". The JSC Members shall instruct the Selected Independent Member to resolve as promptly as practicable but in no event later than thirty (30) days after such Person's appointment on the disputed matter. The Selected Independent Member's determination shall be made based on the submission of documents by the JSC Members unless the Selected Independent Member determines that an oral hearing is necessary. The Selected Independent Member shall determine that which shall be conclusively deemed to be fair and appropriate deadlines for submitting documents and dates, if any, of oral hearings. Each of the JSC Members, or their Representatives, shall pay its own expenses related to this Section 6.5(b). The fees, costs and expenses of the Selected Independent Member shall be borne in full by the JSC Member whose assertion was not accepted by the Selected Independent Member. Any decision rendered by the Selected Independent Member shall be final and binding upon the parties. All proceedings conducted by the Selected Independent Member shall take place in Boston, Massachusetts.

(c) Non-Shelving and Project Return Provisions. Upon such time, if any, that both (x) the Joint Steering Committee or the Selected Independent Member, as applicable, decide to discontinue the Development, and (y) Claudine van der Sande continues to provide services to the Buyer or its Affiliates (including the Company) as an employee or serves as the Seller Representative hereunder, the following provisions shall apply (and, for the avoidance of doubt, if either prong (x) or (y) are not satisfied, the following shall not apply):

(i) if Buyer has developed only one Product and Buyer has developed such Product solely for CHI, Buyer will grant to the Project Return Entity a perpetual, irrevocable, exclusive, worldwide, royalty-bearing license, with the right to sublicense, to develop and commercialize such Product solely for CHI, under a Project Return Agreement. The parties will negotiate in good faith the financial terms for such license, taking into account Buyer's value contribution to such Product, including without limitation the stage of development at the time of shelving or abandonment, all of which terms shall be set forth in the Project Return Agreement. Buyer will retain the right to develop and commercialize all other Products for any and all indications;

(ii) if Buyer has developed more than one Product for more than one indication, and one Product (the "CHI Product") has been developed solely for CHI while the other Product(s) have been developed for non-CHI indication(s), Buyer will grant to the Project Return Entity a perpetual, irrevocable, exclusive, worldwide, royalty-bearing license, with the right to sublicense, to develop and commercialize the CHI Product solely for CHI, under a Project Return Agreement. The parties will negotiate in good faith the financial terms for such license, taking into account Buyer's value contribution to such Product, including without limitation the stage of development at the time of shelving or abandonment, all of which terms shall be set forth in the Project Return Agreement. Buyer will retain the right to develop and commercialize any Product other than the CHI Product for any and all indications;

(iii) if Buyer has developed any Product for both CHI and other indication(s), Buyer will grant to the Project Return Entity a perpetual, irrevocable, exclusive, worldwide, royalty-bearing license, with the right to sublicense, to develop and commercialize such Product solely for CHI but not for any other indication(s), under a Project Return Agreement. The parties will negotiate in good faith (A) the financial terms for such license, taking into account Buyer's value contribution to such Product, including without limitation the stage of development at the time of shelving or abandonment, and (B) the appropriate protections for each party with respect to indication-splitting, regulatory exclusivity, patent rights and other relevant matters. Buyer will retain the right to develop and commercialize such Product for all indications other than CHI, and all other Products for any and all indications; and

(iv) any Project Return Agreement will require Buyer to provide to the Project Return Entity all data, information and materials generated by or for Buyer for Products that are specific to or necessary for the development or commercialization of such Product for CHI, pursuant to detailed provisions set forth in the Project Return Agreement.

(d) Notwithstanding anything to the contrary in this Agreement, the parties hereto agree that the Project Return Agreement shall constitute the sole and exclusive remedy available to the Seller Representative, the Sellers or their successors and assigns with respect to any claim relating to this Section 6.5 or the facts and circumstances relating and pertaining to this Section 6.5.

Section 7.
INDEMNIFICATION

7.1 Representations, Warranties and Covenants. All representations, warranties, covenants, and agreements of the Company, the Sellers and Buyer made in this Agreement, all Ancillary Agreements executed and delivered in connection herewith, and all certificates delivered in connection therewith (i) shall be deemed to have been relied upon by the party or parties to whom they are made, and shall survive the Closing regardless of any investigation on the part of such party or its representatives, and (ii) shall bind the parties' successors and assigns (including, without limitation, any successor to the Company by way of acquisition, merger or otherwise), whether so expressed or not, and, except as otherwise provided in this Agreement, all such representations, warranties, covenants and agreements shall inure to the benefit of the parties (subject to Section 7.2 below) and their respective successors and assigns and to their transferees of Shares, whether so expressed or not.

7.2 Survival Period. Other than with respect to Fundamental Representations, all of the representations and warranties of the Company, the Sellers and Buyer contained in this Agreement shall survive the Closing and continue in full force and effect until the twenty-four (24) month anniversary of the Closing Date, except that any written claim for breach thereof made in good faith with commercially reasonable specificity prior to such expiration date and delivered to the party against whom indemnification is sought shall survive thereafter until finally resolved and, as to any such claim, such applicable expiration will not affect the rights to indemnification of the party making such claim; provided that (i) the Fundamental Representations (other than Section 3.9 (Taxes)) shall survive the Closing and continue in full force and effect until sixty (60) months

following the Closing Date, and (ii) the representations or warranties in Section 3.9 (Taxes) shall survive until the date that is six (6) months after the expiration of the applicable statute of limitations. "Fundamental Representations" shall mean the representations set forth in Section 3.1 (Organization and Good Standing; Organizational Documents), Section 3.2 (Capitalization and Ownership of Shares), Section 3.3 (Company Subsidiaries), Section 3.5(a) (Authority), Section 3.9 (Taxes) and Section 3.16 (Intellectual Property), Section 3.24 (Brokers and Finders) and Section 4.1 (Right to Sell Shares; Binding Effect; Organization and Power). The covenants contained in this Agreement shall survive the Closing until they are otherwise terminated by their respective terms or, if no term is applicable, until the expiration of the statute of limitation in respect of any such claim for the breach of such covenant. It is the express intent of the parties that, if the applicable survival period for an item as contemplated by this Section 7.2 is shorter than the statute of limitations that would otherwise have been applicable to such item, then, by contract, the applicable statute of limitations with respect to such item shall be reduced to the shortened survival period contemplated hereby. The parties further acknowledge and agree that the time periods set forth in this Section 7.2 for the assertion of claims under this Agreement are the result of arms' length negotiation among the parties and that they intend for the time periods to be enforced as agreed by the parties.

7.3 Limitation on the Sellers' Liability. The liability of the Sellers in respect of any breach by the Sellers of the representations and warranties of the Sellers or another provision of this Agreement shall be limited as follows:

(a) In respect of any breach by the Sellers of the representations and warranties of the Sellers (other than the Fundamental Representations) or another provision of this Agreement to USD 500,000 *plus* 10% of any Milestone Payments actually paid to the Seller Representative (for further distribution to the Sellers in accordance with the Distribution Methodology), whereby the sole recourse of the Buyer shall be the Holdback Amount and its right of sett-off against any payment obligations of the Buyer to the Sellers in relation to the Milestone Payments; and

(b) In respect of any breach by the Sellers of the Fundamental Representations to the Aggregate Purchase Price actually paid or payable to the Sellers.

7.4 Indemnification Provisions for Buyer's Benefit. Provided that Buyer makes a written claim for indemnification, describing in commercially reasonable detail the facts and circumstances with respect to the subject matter of such claim within the applicable survival period set forth in Section 7.2, subject to the limitations set forth in this Section 7, each Seller severally, and not jointly, based on their Pro Rata Portion, on his or her own behalf and on behalf of his or her successors, executors, administrators, estate, heirs and assigns (collectively, for the purposes of this Section 7.4, the "Seller Indemnifying Parties", and each individually, a "Seller Indemnifying Party") shall indemnify Buyer and Buyer's directors, managers, officers, employees, affiliates, direct and indirect partners, shareholders, agents, attorneys, Representatives, successors and assigns (collectively, the "Buyer Indemnified Parties") from and against the entirety of any Losses of any of Buyer Indemnified Parties arising out of, or by reason of:

(a) any breach by the Sellers of the representations and warranties of the Company and the Sellers (other than the Fundamental Representations);

(b) any breach by the Sellers of the Fundamental Representations of the Company and the Sellers;

(c) any breach by the Sellers of any covenant made by the Sellers under this Agreement;

(d) fraud, intentional misrepresentation or willful misconduct;

(e) any (i) Tax liabilities of the Company or predecessors with respect to any Pre-Closing Tax Period; (ii) Taxes of the Sellers (including, without limitation, Taxes arising as a result of the transactions contemplated by this Agreement) or any of their Affiliates (excluding Company) for any Tax period; (iii) Taxes for which the Company (or any predecessor) is held liable under Section 34 and/or 35 of the Dutch Tax Collection Act (*Invorderingswet 1990*); (iv) Taxes for which the Company (or any predecessor) is held liable by reason of being included in any consolidated, affiliated, combined or unitary group at any time on or before the Closing Date; (v) Taxes imposed on or payable by third parties with respect to which the Company has an obligation to indemnify such third party pursuant to a transaction consummated on or prior to the Closing; and (vi) any Taxes of the Company or the Sellers imposed on Buyer or any of its affiliates as a withholding Tax with respect to payments pursuant to this Agreement; provided, however, that the Seller Indemnifying Parties shall have no liability under this Section 7.4(e) for any Taxes to the extent they were treated as Company Debt;

(f) any Company Debt or Seller Transaction Expenses charged to the Buyer, the Company or any of their Affiliates (following the adjustment as set forth in Section 2.5); and

(g) any misrepresentation, error or inaccuracy in the information contained in the Distribution Methodology; and

(h) any liabilities arising from the repayment of the Convertible Loan Agreements.

Notwithstanding anything provided in this Agreement to the contrary, no indemnification shall be payable by the Sellers pursuant to Section 7.4 with respect to any claim asserted by a Buyer Indemnified Party after the expiration of the survival period, if any, prescribed for such representation, warranty or covenant in Section 7.2. Other than in respect of Losses pursuant to Section 7.4(d) and Section 7.4(e), (i) a Seller Indemnifying Party's several liability for a Loss shall be determined based upon each Seller's Pro Rata Portion of the Aggregate Purchase Price and (ii) in no event shall the aggregate liability of the Sellers for indemnification payable under this Section 7 exceed an amount equal to the Aggregate Purchase Price.

7.5 Indemnification Provisions for the Sellers' Benefit; Limitations.

(a) Subject to the provisions of this Section 7, from and after Closing, Buyer agrees to indemnify and hold the Sellers and their employees, directors, managers, officers, partners or shareholders, Representatives, affiliates, and their respective successors and assigns (the "Seller Indemnified Parties") harmless from and against any Losses sustained or suffered by the Seller Indemnified Parties to the extent caused by or arising from a breach of any representation or warranty made by Buyer, the fraud, intentional misrepresentation or willful misconduct of Buyer, or a failure to perform any covenant or agreement made by Buyer herein.

(b) Notwithstanding anything provided in this Agreement to the contrary, no indemnification shall be payable by Buyer pursuant to Section 7.5(a) with respect to any claim asserted by a Seller Indemnified Party after the expiration of the survival period, if any, prescribed for such representation, warranty or covenant in Section 7.2. In no event shall the aggregate liability of Buyer for indemnification payable under this Section 7 exceed an amount equal to the Aggregate Purchase Price.

7.6 Tax Treatment of Indemnity Payments. Any indemnity payment made pursuant to this Section 7 shall to the greatest extent permitted by applicable law be treated as an adjustment to the purchase price for all Tax purposes and shall be reported as such by Sellers and Buyer on their Tax Returns.

7.7 Matters Involving Third Parties.

(a) If any third party notifies any party (the "Indemnified Party") with respect to any matter (a "Third-Party Claim") that gives rise to a claim for indemnification against another party (the "Indemnifying Party") under this Section 7, then the Indemnified Party shall promptly (and in any event within fifteen (15) Business Days after receiving notice of the Third-Party Claim) notify the Indemnifying Party thereof in writing (a "Notice"); provided, however, that failure to give such Notice shall not limit the right of an Indemnified Party to recover indemnity or reimbursement from any Indemnifying Party except to the extent that such Indemnifying Party suffers any material prejudice or material harm with respect to such claim as a result of such failure except and to the extent that the Indemnifying Party can demonstrate actual loss or actual prejudice (and in any event, solely to the extent of such loss or prejudice) as a result of such failure. For the avoidance of doubt, this Section 7.7 shall not apply with respect to any cooperation on Tax matters, which shall be governed solely by Section 8.2.

(b) In the case of any Third-Party Claims for which indemnification is sought, the Indemnifying Party shall be entitled at its cost and expense to (i) conduct and control any proceedings or negotiations with such third party, (ii) perform and control or direct the performance of any required activities, (iii) take all other steps to settle or defend any such claim (provided that the Indemnifying Party shall not settle any such claim without the consent of the Indemnified Party (which consent shall not be unreasonably withheld, conditioned or delayed) unless the settlement includes a complete release of the Indemnified Party with respect to the claim and no additional obligation, restriction or Losses shall be imposed on the Indemnified Party other than solely the payment of money damages for which the Indemnified Party will be indemnified hereunder) and (iv) employ counsel to contest any such claim or liability; provided that the Indemnifying Party shall not have the right to assume control of such defense, if the claim for which the Indemnifying Party seeks to assume control: (w) seeks non-monetary relief (except where non-monetary relief is merely incidental to a primary claim or claims for monetary damages), (x) involves criminal allegations, (y) is one in which the Indemnifying Party is also a party and for which joint representation would, in the reasonable opinion of the Indemnified Party's or Indemnifying Party's respective counsel, be inappropriate or, in the reasonable opinion of the Indemnified Party's or Indemnifying Party's respective counsel, there may be legal defenses available to the Indemnified Party that are materially different from or materially additional to those available to the Indemnifying Party or (z) involves a claim for which, upon petition by the Indemnified Party, the appropriate court rules that the Indemnifying Party failed or is failing to

vigorously prosecute or defend; provided that if the Indemnifying Party is the Sellers, such Indemnifying Party shall not have the right to defend or direct the defense of any such Third-Party Claim that is asserted directly by or on behalf of a Person that is a current supplier or customer of the Company. The Indemnifying Party shall, within thirty (30) days after delivery of the Notice to Indemnifying Party (or sooner, if the nature of the Third-Party Claim so requires) (the "Dispute Period"), notify the Indemnified Party of its intention as to the conduct and control of the defense of such claim, provided that the Indemnified Party and its counsel shall cooperate with the Indemnifying Party and its counsel. Until the Indemnified Party has received notice of the Indemnifying Party's election whether to defend any claim, the Indemnified Party shall take commercially reasonable steps to defend (but may not settle) such claim. If the Indemnifying Party shall decline to assume the defense of any such claim, or the Indemnifying Party shall fail to notify the Indemnified Party within the Dispute Period of the Indemnifying Party's election to defend such claim, the Indemnified Party shall defend against such claim (provided that the Indemnified Party shall not settle such claim without the consent of the Indemnifying Party (which consent shall not be unreasonably withheld, conditioned or delayed)) and the Indemnifying Party will remain responsible for any Losses the Indemnified Party may suffer as a result of such Third-Party Claim to the extent subject to indemnification under this Section 7. If the Indemnifying Party assumes the defense of any Third-Party Claim in accordance with the provisions of this Section 7.7, then the Indemnifying Party shall be liable for the reasonable fees of one other counsel or any other reasonably incurred expenses with respect to the defense of such Third-Party Claim incurred by Indemnified Party following the assumption of such defense by Indemnifying Party.

7.8 Direct Claims. Any indemnification claim by an Indemnified Party which does not result from a Third-Party Claim shall be asserted by the Indemnified Party by giving the Indemnifying Party and the Seller Representative prompt written notice thereof. Such written notice shall summarize the basis for the indemnification claim based on the information reasonably available at that time to the Indemnified Party. The failure to give written notice shall not, however, relieve the Indemnifying Party of its indemnification obligations, unless, and then solely to the extent that, the rights of the parties from whom indemnity is sought are materially prejudiced as a result of such failure; provided, however, that no such notice shall have any effect or be valid if it is given following the end of any applicable survival period provided for in Section 7.2. The Indemnifying Party shall have thirty (30) days after its receipt of such notice to respond in writing to such claim. If the Indemnifying Party does not so respond within such thirty (30) day period, the Indemnifying Party shall be deemed to have accepted such claim, in which case the Indemnified Party shall be free to pursue such remedies as may be available to the Indemnified Party on the terms and subject to the provisions of this Agreement and the Indemnifying Party shall promptly pay any amounts owed in accordance with the terms of this Agreement.

7.9 Further Limitations and Qualifications.

(a) Priority of Recovery. Without limiting the other clauses of this Section 7, any Losses pursuant to Section 7.4 for which any Buyer Indemnified Party is entitled to indemnification pursuant to the terms of this Agreement shall be satisfied in the following order:

(i) first, through set off against the Holdback Amount;

(ii) second, in the event of Losses that exceed the then available Holdback Amount or the exhaustion or prior release of the Holdback Amount, through set off against the Milestone Payments, if any, related to the Milestones that have been finally determined to be achieved in accordance with Section 2.9 and that have not been paid to the Seller Representative (on behalf of the Sellers) (the "Undistributed and Earned Milestone Payments"); and

(iii) third, in the event of Losses that exceed the then available Undistributed and Earned Milestone Payments, directly from the Seller Indemnifying Parties in accordance with their Pro Rata Portion.

7.10 Holdback Arrangements.

(a) The Holdback Amount shall be available to compensate the Buyer Indemnified Parties for any claims by such parties for any Losses suffered or incurred by them and for which they are entitled to recovery under this Section 7, which compensation will occur through the forfeiture of the Holdback Amount in accordance with the terms of this Section 7.10. Each claim for Losses that is to be satisfied through the forfeiture of a portion of the Holdback Amount pursuant to this Section 7 shall be satisfied, as to each Seller Indemnifying Party, by the forfeiture of such portion of the Holdback Amount with a value equal to such Seller Indemnifying Party's Pro Rata Portion of the Losses.

(b) Except as set forth below, the period during which claims for Losses to be satisfied through the forfeiture of all or any portion of the Holdback Amount may be made under this Agreement shall commence at the Closing and continue through the one (1) year anniversary of the Closing (the "Holdback Period"). On or before the tenth (10th) Business Day following the end of the Holdback Period, Buyer shall release to the Seller Representative for further distribution to the Sellers (in accordance with their Pro Rata Portion) a portion of the Holdback Amount equal to (i) the then-remaining Holdback Amount that has not been previously forfeited in satisfaction of indemnified Losses or pursuant to Section 2.5(g), minus (ii) an amount (such amount, an "Unresolved Claim Amount") sufficient in Buyer's reasonable estimation to satisfy any unresolved claims (each, an "Unresolved Claim") specified in a certificate executed and delivered by Buyer to the Seller Representative prior to the end of the Holdback Period. Any such Unresolved Claim Amount shall be retained pending final resolution of the applicable Unresolved Claim. Upon a Final Determination (as defined below) of the applicable Unresolved Claim, (x) to the extent such Unresolved Claim is finally determined to result in a payment to a Buyer Indemnified Party, such finally determined amount (if any) of the Unresolved Claim Amount shall be retained by Buyer for distribution to the applicable Buyer Indemnified Party, and (y) the remainder of the Unresolved Claim Amount (if any) shall be distributed to the Seller Representative for further distribution to the Sellers in accordance with their Pro Rata Portion.

(c) In the event that there exist Unresolved Claims as of the expiration of the Holdback Period, as soon as all such Unresolved Claims have been resolved, Buyer shall promptly, and in any event within twenty (20) Business Days following the resolution or satisfaction of the last of such Unresolved Claims, deliver in accordance with Section 7.10(d), the remaining portion of the Holdback Amount then retained by Buyer, if any, that has not been forfeited in satisfaction of such Unresolved Claims in accordance with this Section 7.10.

(d) Each release of the Holdback Amount to the Seller Representative on behalf of the Sellers pursuant to this Section 7.10 shall be made by Buyer to Seller Representative, and Seller Representative shall distribute such amount to the Sellers in proportion to the Seller's respective Pro Rata Portion of the Holdback Amount being released, subject to appropriate adjustments to take into account any fraud, intentional misrepresentation or willful misconduct, or actual knowledge thereof, by any Seller.

7.11 Set-Off Right. Notwithstanding anything to the contrary in this Agreement, but, in the case of indemnifications claims, subject to the limitations on indemnification in this Section 7, Buyer shall be entitled to set-off Losses for which a Buyer Indemnified Party is entitled to indemnification pursuant to Section 7.4 ("Set-Off Rights") or pursuant to Section 2.5(g), but solely following (i) final resolution of the indemnification claim by mutual written agreement of Buyer and the Seller Representative, or (ii) otherwise pursuant to a final non-appealable order or judgment by a court of competent jurisdiction ((i) or (ii), together, a "Final Determination"), in either case, against any payments, including any Milestone Payments, required to be made by Buyer pursuant to this Agreement following the Closing (a "Post-Closing Payment Set-Off"). Any such Post-Closing Payment Set-Off shall be in accordance with each Seller's applicable Pro Rata Portion. If any Unresolved Claim remains unresolved as of the date any payment, including any Milestone Payment, pursuant to this Agreement would otherwise be due to the Sellers, then Buyer may retain and holdback such amount (but in no event more than the amount of any such Unresolved Claims), to be held by Buyer in a separate segregated account (the "Set-Off Account"). Any such amount shall be held pending final resolution of the applicable Unresolved Claim. Upon a Final Determination of the applicable Unresolved Claim, (x) to the extent such Unresolved Claim is finally determined to result in a payment to a Buyer Indemnified Party, such finally determined amount (if any) shall be distributed to such Buyer Indemnified Party out of the Set-Off Account and (y) the remainder of the Set-Off Account shall be distributed to the Sellers in accordance with their Pro Rata Portion.

7.12 Exclusive Remedies. Subject to (and without limiting the effects of) the terms of Section 10.7, from and after Closing, except with respect to matters covered by Section 2.5 or Section 2.9, the remedies provided in this Section 7 shall constitute the sole and exclusive remedies available to any party hereto with respect to any claim relating to this Agreement or the transactions contemplated hereby and the facts and circumstances relating and pertaining hereto (whether any such claim shall be made in contract, breach of warranty, tort or otherwise), other than for fraud.

7.13 Duration of Claim. The indemnification obligations of the Indemnifying Party pursuant to this Agreement with respect to a specific claim for which indemnification is provided under this Agreement shall extend beyond the time period for indemnification set forth herein with respect to such specific claim until it has been fully discharged or resolved or settled so long as a written notice prepared in good faith with reasonable specificity (to the extent known at such time) shall have been given to the Indemnifying Party on or prior to the end of such time period.

Section 8.
TAXES

8.1 Tax Returns and Tax Matters. Buyer shall prepare or cause to be prepared, and file or cause to be filed, any and all Tax Returns of or with respect to the Company for any Pre-Closing

Tax Period ("Pre-Closing Tax Returns"). At least twenty (20) days prior to filing a Pre-Closing Tax Return, Buyer shall submit a copy of such Tax Return to Seller Representative for Seller Representative's review and comment, and Buyer shall consider in good faith any reasonable comments to such Tax Returns as are provided by Seller Representative at least five (5) days prior to filing of such Tax Returns. Seller Representative and Buyer (and each of their respective Affiliates) will give written notice to each other of any Audit with respect to the Company for any Pre-Closing Tax Period (a "Tax Contest") within thirty (30) days of receipt of notice from a Tax Authority of such Tax Contest. Buyer will control the conduct of all Tax Contests; provided, however, that Buyer will not settle or otherwise compromise such Tax Contest without the prior written consent of the Seller Representative (such consent not to be unreasonably withheld, conditioned or delayed) to the extent such settlement or compromise would reasonably be expected to result in an indemnification claim pursuant to Section 7.4(e). In the event of any conflict or overlap between any other provision in this Agreement and the provisions of this Section 8.1, the provisions of this Section 8.1 shall control. Notwithstanding anything in this Agreement to the contrary, Buyer, in its sole discretion, may make an election pursuant to Section 338(g) of the Code with respect to the Acquisition.

8.2 Cooperation. Seller Representative, the Company and Buyer (or their respective duly authorized agents) agree to furnish or cause to be furnished to the other party, upon request, as promptly as practicable, such information and assistance relating to Taxes, including, without limitation, access to books and records, as is reasonably necessary for the preparation and filing of any of the Sellers' Tax Returns. The parties shall retain, and shall cause the Company to retain, all books and records with respect to Taxes for Pre-Closing Tax Periods until the earlier of (i) the expiration of the applicable statute of limitations or (ii) the sixth (6th) anniversary of the Closing Date.

8.3 Transfer Taxes. All Transfer Taxes incurred in connection with the transactions contemplated hereby shall be borne (i) 50% by the Buyer and (ii) 50% by the Sellers. The Sellers and the Seller Representative shall reasonably cooperate with Buyer in the preparation and filing of any Tax Returns required to be filed with respect to such Transfer Taxes.

Section 9.
SELLER REPRESENTATIVE

9.1 Appointment of Seller Representative.

(a) Each Seller irrevocably appoints and authorizes Thudaumot Holding, B.V. as the "Seller Representative" and in such capacity as its agent and attorney-in-fact to take such action as agent and attorney-in-fact on its behalf and to exercise such powers under this Agreement and any Ancillary Agreements which require any form of Seller approval or consent, together with all such powers as are reasonably incidental thereto. Seller Representative may perform its duties as such through sub-agents and attorneys-in-fact and shall have no liability for any acts or omissions of any such sub-agent or attorney if selected by it with reasonable care. Buyer and each Buyer Indemnified Person shall be entitled to deal exclusively with Seller Representative on behalf of any and all Sellers with respect to all matters relating to this Agreement and the Ancillary Agreements, and shall be entitled to rely conclusively (without further evidence of any kind whatsoever) on any document executed or purported to be executed on behalf of any Seller by

Seller Representative, and on any other action taken or purported to be taken on behalf of any Seller by Seller Representative, as fully binding upon such Seller, and Buyer shall have no liability as a result of any such reliance.

(b) Without limiting the generality of the foregoing in Section 9.1(a), Seller Representative, acting alone without the consent of any Seller, is hereby authorized to (i) take any and all actions under Section 2, (ii) effect payments to the Sellers hereunder, (iii) receive and/or give notices hereunder, (iv) receive and/or make payment hereunder, (v) execute waivers and/or amendments hereof, and/or (vi) execute and deliver documents, releases and/or receipts hereunder.

(c) The parties confirm their understanding that Seller Representative is an affiliate of the Sellers, and that it shall have the same rights and powers under this Agreement as any other Seller and may exercise or refrain from exercising the same as though it were not Seller Representative.

(d) Seller Representative may consult with legal counsel, independent public accountants and other experts selected by it and shall not be liable to any Seller for any action taken or omitted to be taken by it in good faith in accordance with the advice of such counsel, accountants or experts.

(e) Seller Representative shall not be liable to any Seller for (i) any act or omission consented to or requested by any Seller, or (ii) any act or omission otherwise taken by it hereunder except, in the case of this clause (ii) only, for willful misconduct by Seller Representative. Seller Representative shall not be deemed to be a trustee or other fiduciary on behalf of any Seller or any other Person, nor shall Seller Representative have any liability in the nature of a trustee or other fiduciary. Seller Representative does not make any representation or warranty as to, nor shall it be responsible for or have any duty to ascertain, inquire into or verify (A) any statement, warranty or representation made in or in connection with this Agreement or the Ancillary Agreements, (B) the performance or compliance with any of the covenants or agreements of Sellers under this Agreement or any of the other Ancillary Agreements, or (C) the genuineness, legality, validity, binding effect, enforceability, value, sufficiency, effectiveness or genuineness of this Agreement, the Ancillary Agreements or any other instrument or writing furnished in connection herewith or therewith. Seller Representative shall not incur any liability by acting in reliance upon any notice, consent, certificate, statement or other writing (which may be a bank wire, facsimile or similar writing) believed by it to be genuine and to be signed or sent by the proper party or parties.

(f) Each Seller shall pay or reimburse Seller Representative, upon presentation of an invoice, for all fees, costs and expenses incurred by Seller Representative (including, without limitation, fees and expenses of counsel to Seller Representative) in connection with (i) the enforcement of this Agreement and any of the Ancillary Agreements and/or the protection or preservation of the rights of each Seller and/or Seller Representative against Buyer, or any of their respective assets, and (ii) any amendment, modification or waiver of any of the terms of this Agreement or any Ancillary Agreements (whether or not any such amendment, modification or waiver is signed or becomes effective). Such amounts shall first be paid out of an advance amount equal to $25,000 (the "Advance Amount"), which shall be delivered by Buyer to Seller Representative at the Closing as a deduction from the Purchase Price, which Seller Representative

shall maintain in a separate account for application under this Section 9.1. The Advance Amount shall be treated as received and voluntarily set aside by the Sellers at Closing.

(g) Each Seller shall indemnify, defend and hold harmless Seller Representative and Seller Representative's Affiliates and their respective partners, directors, officers, managers, members, agents, attorneys, employees and shareholders of each of the foregoing against any claim that such indemnitees may suffer or incur in connection with its capacity as the Seller Representative, or any act or omission by such indemnitees hereunder or under the Ancillary Agreements (except such resulting from such indemnitees' willful misconduct).

(h) Each Seller acknowledges that it has, independently and without reliance upon Seller Representative, and based on such documents and information as it has deemed appropriate, made its own legal analysis and decision to enter into this Agreement. Each Seller also acknowledges that it will, independently and without reliance upon Seller Representative, and based on such documents and information as it shall deem appropriate at the time, continue to make its own decisions in taking or not taking any action under this Agreement.

(i) Seller Representative may resign at any time by giving notice thereof to the Sellers. Upon any such resignation, Sellers shall appoint a successor Seller Representative. If no successor Seller Representative shall have been appointed by Sellers and shall have accepted such appointment within thirty (30) days after the retiring Seller Representative gives notice of resignation, then the retiring Seller Representative, may, on behalf of Sellers, appoint a successor Seller Representative. Upon the acceptance of its appointment as Seller Representative hereunder by a successor Seller Representative, such successor Seller Representative shall thereupon succeed to, and become vested with, all the rights and duties of the retiring Seller Representative, and the retiring Seller Representative shall be discharged from its duties and obligations hereunder. After the retiring Seller Representative's resignation hereunder as Seller Representative, the provisions of this Agreement shall inure to its benefit as to any actions taken or omitted to be taken by it while it was Seller Representative.

(j) Seller Representative shall not be required by Sellers to institute or be permitted to defend any action involving any matters referred to herein or which affects it or its duties or liabilities hereunder, unless or until requested to do so by any party to this Agreement and then only upon receiving full indemnity, in character satisfactory to Seller Representative, against any and all claims, liabilities and expenses, including reasonable attorneys' fees, in relation thereto.

(k) This Section 9.1 sets forth all of the duties of Seller Representative to the Sellers with respect to any and all matters pertinent hereto. No implied duties or obligations shall be read into this Agreement or any of the Ancillary Agreements against Seller Representative. The obligations of Seller Representative hereunder and under the Ancillary Agreements are only those expressly set forth herein and therein.

(l) Seller Representative shall disburse any remaining Advance Amount to the Sellers at such time that it determines in its sole discretion that it is no longer necessary to hold such funds.

(m) Notwithstanding anything to the contrary in this Agreement, only the Seller Representative, and not any Sellers, will have the right to assert a claim or institute an Action pursuant any Seller's rights hereunder.

Section 10.
MISCELLANEOUS

10.1 Notices. All notices, requests, demands, consents and communications necessary or required under this Agreement shall be delivered by hand or sent by registered or certified mail, return receipt requested, by overnight prepaid courier or by e-mail to:

If to Buyer, or following Closing, to the Company:

Rhythm Pharmaceuticals Netherlands B.V.
c/o Rhythm Pharmaceuticals, Inc.
222 Berkeley Street, Suite 1200
Boston, MA 02116
Attention: Jim Flaherty
Telephone: 857-254-4474
Email: jflaherty@rhythmtx.com

with a copy (which shall not constitute notice) to:

Latham & Watkins LLP
200 Clarendon Street, 27th Floor
Boston, Massachusetts 02116
Attention: Peter Handrinos; Gloria Ring
Telephone: (617) 948-6000
Email: peter.handrinos@lw.com; gloria.ring@lw.com

If to Seller Representative:

Thudaumot Holding B.V.
Omval 84
1096 HW Amsterdam
The Netherlands
Attention: Claudine van der Sande
Email: c.vandersande@xinvento.co

with a copy (which shall not constitute notice) to:

Allen & Overy LLP
Apollolaan 15, 1077 AB Amsterdam
The Netherlands
Attention: Christiaan de Brauw, Berend Veenstra
Telephone: +31 (0) 20 674 1552
Email: Christiaan.deBrauw@AllenOvery.com;
Berend.Veenstra@AllenOvery.com

If to any Seller:

Such address listed on the Company's books and records.

All such notices, requests, demands, consents and other communications shall be deemed to have been duly given or sent three (3) days following the date on which mailed, or one (1) day following the date mailed if sent by overnight courier, or on the date on which delivered by hand or by email or other electronic transmission, as the case may be, and addressed as aforesaid. Any notice to be given to any Seller hereunder shall be given to Seller Representative or, if for any reason there ceases to be a Seller Representative, to each Seller.

10.2 Notary. The parties are aware of the fact that the Notary works with NautaDutilh. With reference to the Code of Conduct (*Verordening beroeps- en gedragsregels*) established by the Royal Notarial Professional Organization (*Koninklijke Notariële Beroepsorganisatie*), the parties hereby explicitly agree that the Notary shall execute any notarial deeds related to this Agreement.

10.3 Successors and Assigns. All covenants and agreements and other provisions set forth in this Agreement and made by or on behalf of any of the parties hereto shall bind and inure to the benefit of the successors, heirs and permitted assigns of such party, whether or not so expressed. None of the parties may assign, transfer or delegate any of their respective rights or obligations under this Agreement, by operation of law or otherwise, without the consent in writing of the Company (or the Seller Representative from and after the Closing) and Buyer. Any purported assignment or delegation of rights or obligations in violation of this Section 10.3 is void and of no force or effect.

10.4 No Joint Seller Obligations. The obligations of each of the Sellers under this Agreement are several and not joint obligations. For the avoidance of doubt, and without derogating from the generality of the aforegoing, a Seller shall not be liable for any breach by any other Seller under any of the representations and warranties of the Sellers set forth in Section 4.

10.5 Severability. In the event that any one (1) or more of the provisions contained herein is held invalid, illegal or unenforceable in any respect for any reason in any jurisdiction, the validity, legality and enforceability of any such provision in every other respect and of the remaining provisions hereof shall not be in any way impaired or affected (so long as the economic or legal substance of the transactions contemplated hereby is not affected in any manner materially adverse to any party), it being intended that each of the parties' rights and privileges shall be enforceable to the fullest extent permitted by applicable Legal Requirements, and any such invalidity, illegality and unenforceability in any jurisdiction shall not invalidate or render unenforceable such provision in any other jurisdiction (so long as the economic or legal substance of the transactions contemplated hereby is not affected in any manner materially adverse to any party). If any court of competent jurisdiction determines that any provision of this Agreement is invalid, illegal or unenforceable, such court has the power to fashion and enforce another provision (instead of the provision held to be invalid, illegal or unenforceable) that is valid, legal and enforceable and carries out the intentions of the parties hereto under this Agreement and, in the event that such court does not exercise such power, the parties hereto shall negotiate in good faith in an attempt to agree to another provision (instead of the provision held to be invalid, illegal or

unenforceable) that is valid, legal and enforceable and carries out the parties' intentions to the greatest lawful extent under this Agreement.

10.6 Third Parties. Except as specifically set forth or referred to herein, nothing herein expressed or implied is intended or shall be construed to confer upon or give to any Person, other than the parties hereto and their permitted successors and assigns, any rights or remedies under or by reason of this Agreement or any other certificate, document, instrument or agreement executed in connection herewith nor be relied upon other than the parties hereto and their permitted successor or assigns.

10.7 Specific Performance. The parties agree that irreparable damage would occur in the event that any of the provisions of this Agreement were not performed in accordance with their specific terms or were otherwise breached and that money damages or other legal remedies would not be an adequate remedy for any such breach. It is accordingly agreed that: (a) the Buyer shall be entitled to an injunction, specific performance and other equitable relief to prevent or restrain breaches or threatened breaches of this Agreement by the Seller Representative and to enforce specifically all of the terms and provisions hereof, and (b) Seller Representative (on behalf of the Sellers) shall be entitled to an injunction or injunctions to prevent or restrain breaches or threatened breaches by Buyer. Subject to the limitations set forth in this Section 10.7, Sellers (on behalf of themselves) and the Seller Representative, on the one hand, and the Buyer, on the other hand, hereby agree not to raise any objections to the availability of the equitable remedy of specific performance to prevent or restrain breaches or threatened breaches of the provisions of this Agreement identified above in this Section 10.7 by such party.

10.8 No Rescission. To the extent permitted by law, the parties waive their rights, if any, to (i) in whole or in part annul, rescind or dissolve (including any *gehele dan wel partiële ontbinding en vernietiging*) this Agreement, and (ii) invoke Sections 6:228 and 6:230 of the Dutch Civil Code in the sense that an error (*dwaling*) shall remain for the risk and account of the party in error as referred to in Section 6:228, subsection 2 of the Dutch Civil Code. The applicability of the provisions under Title 1 of Book 7 and Article 89 of Book 7 of the Dutch Civil Code are hereby expressly excluded (to the extent these provisions do not contain mandatory law). In the event of a breach of the representations and warranties made under this Agreement the only remedy for the Buyer shall be a claim for damages and not for specific performance (*nakoming*).

10.9 Governing Law. This Agreement (including, for the avoidance of doubt, Section 10.10) and any contractual or non-contractual obligations arising out of or in connection to it, is governed by and shall be construed in accordance with the laws of the Netherlands.

10.10 Dispute Resolution. Any dispute arising out of or in connection with this Agreement (including any dispute as to the validity of this Agreement, any questions in respect of the authority of the arbitrators and any dispute about whether a particular dispute should be referred to arbitration) will be finally settled by arbitration in accordance with the rules of the Netherlands Arbitration Institute (*Nederlands Arbitrage Instituut*). The arbitral tribunal will be composed of three arbitrators appointed in accordance with those rules. The place of the arbitration will be Amsterdam, the Netherlands. The language of the arbitration will be English. The arbitrators will decide according to the rules of law. Their arbitral award will not be disclosed other than to the parties to the arbitral proceedings. Consolidation of arbitral proceedings with other proceedings as

provided for in article 1046 of the Dutch Code of Civil Procedure is excluded. Notwithstanding the foregoing, nothing in this Section 10.10 shall preclude the parties from applying for injunctive relief in summary proceedings (*kort geding*) before any competent court instead of arbitrators. This Section 10.10 shall also apply to disputes arising out of or in connection with agreements which are connected with this agreement, unless the relevant agreement expressly provides otherwise.

10.11 Fees and Expenses. Except as otherwise provided in this Agreement, (a) $25,000 of the total fees, costs and expenses of the Sellers incurred in connection with this Agreement and the transactions contemplated hereby, including fees and expenses of financial advisors, financial sponsors, legal counsel and other advisors, shall be paid by Buyer subject to the consummation of the Closing, (b) all remaining fees, costs and expenses of the Company, the Seller Representative and Sellers incurred in connection with this Agreement and the transactions contemplated hereby, in each case including fees and expenses of financial advisors, financial sponsors, legal counsel and other advisors, shall be paid by the Company (but subject to the inclusion of any such amounts in the Seller Transaction Expenses), and (c) all fees, costs and expenses of Buyer incurred in connection with this Agreement and the transactions contemplated hereby, in each case including fees and expenses of financial advisors, financial sponsors, legal counsel and other advisors, shall be paid by the Buyer; provided that, notwithstanding the foregoing, (i) the Sellers shall be responsible for a portion of any Transfer Taxes incurred in connection with the transactions contemplated hereby in accordance with Section 8.3, (ii) any fees of the Accounting Arbitrator shall be borne by the parties as provided in Section 2.5(f), (iii) any fees of the Selected Regulatory Expert or the Accounting Expert shall be borne by the parties as provided in Section 2.9, and (iv) any fees of the Selected Independent Member shall be borne by the parties are provided in Section 6.5.

10.12 Entire Agreement; Not Binding Until Executed. This Agreement (including the Disclosure Schedule, Schedules and Exhibits) and the other agreements referred to herein (including the Ancillary Agreements) is complete, and all promises, representations, understandings, warranties and agreements with reference to the subject matter hereof, and all inducements to the making of this Agreement relied upon by all the parties hereto, have been expressed herein or in such Disclosure Schedule, Schedules, Exhibits or such other agreements and this Agreement, including such Disclosure Schedule, Schedules, Exhibits and such other agreements, supersedes any prior understandings, negotiations, agreements or representations by or among the parties, written or oral, to the extent they relate in any way to the subject matter hereof or thereof. Neither this Agreement nor any of the terms or provisions hereof are binding upon or enforceable against any party hereto unless and until the same is executed and delivered by all of the parties hereto.

10.13 Amendments; No Waiver. Subject to applicable Legal Requirements, any provision of this Agreement may be amended or waived if, but only if, such amendment or waiver is in writing and is signed, in the case of an amendment, by Buyer and the Seller Representative, or, in the case of a waiver, by each party against whom the waiver is to be effective; provided that the Seller Representative shall have the authority to sign any such waiver on behalf of Seller. No course of dealing and no failure or delay on the part of any party hereto in exercising any right, power or remedy conferred by this Agreement shall operate as a waiver thereof or otherwise prejudice such party’s rights, powers and remedies. The failure of any of the parties to this Agreement to require the performance of a term or obligation under this Agreement or the waiver

by any of the parties to this Agreement of any breach hereunder shall not prevent subsequent enforcement of such term or obligation or be deemed a waiver of any subsequent breach hereunder. No single or partial exercise of any right, power or remedy conferred by this Agreement shall preclude any other or further exercise thereof or the exercise of any other right, power or remedy.

[Remainder of Page Intentionally Blank; Signature Pages Follow]

IN WITNESS WHEREOF, the parties hereto have caused this Agreement to be executed and delivered on the date first set forth above.

BUYER:

RHYTHM PHARMACEUTICALS NETHERLANDS B.V.
By: _____
Name: Jim Flaherty
Title: Authorized Signatory

[Signature Page to Share Purchase Agreement]

COMPANY:

Name: Claudine van der Sande
for and on behalf of
THUDAUMOT HOLDING B.V.
for and on behalf of
XINVENTO B.V.

[Signature Page to Share Purchase Agreement]

SELLERS:

Name: Claudine van der Sande
for and on behalf of
THUDAUMOT HOLDING B.V.

PIET WIGERINCK

Name: Claudine van der Sande
for and on behalf of
XINVENTO B.V.
for and on behalf of
STICHTING ADMINISTRATIEKANTOOR XINVENTO

[Signature Page to Share Purchase Agreement]

SELLER REPRESENTATIVE:

Name: Claudine van der Sande
for and on behalf of
THUDAUMOT HOLDING B.V.

[Signature Page to Share Purchase Agreement]

SCHEDULE A

LIST OF SELLERS; SHARES IMMEDIATELY PRIOR TO CLOSING; PRO RATA PORTION

Seller	Shares	Pro Rata Portion
Thudaumot Holding B.V.	10,000	66.7%
Piet Wigerinck	3,333	22.2%
Stichting Administratiekantoor Xinvento	1,667	11.1%
Total	**15,000**	**100.00%**

SCHEDULE 2.2

FORM OF DEED OF TRANSFER

[See attached.]

SCHEDULE 2.5(C)(VI)

DISTRIBUTION METHODOLOGY

[See attached.]

SCHEDULE 2.7(M)

CONVERTIBLE LOAN AGREEMENT HOLDERS

[See attached.]

DISCLOSURE SCHEDULE

[See attached.]

EXHIBIT A

FORM OF CLA WAIVER AND RELEASE

[See attached.]

EXHIBIT B

DEVELOPMENT PLAN

[See attached.]

Exhibit 4.3

DESCRIPTION OF THE REGISTRANT'S SECURITIES REGISTERED PURSUANT TO SECTION 12 OF THE SECURITIES EXCHANGE ACT OF 1934

As of December 31, 2022, Rhythm Pharmaceuticals, Inc. ("we," "our," "us," or the "Company") had one class of securities registered under Section 12 of the Securities Exchange Act of 1934, as amended: common stock, par value $0.001 per share.

The following description of our capital stock is a summary, does not purport to be complete and is subject to, and qualified in its entirety by reference to, our amended and restated certificate of incorporation and amended and restated bylaws, each of which has been publicly filed with the Securities and Exchange Commission, and the terms and provisions of the Delaware General Corporation Law, or DGCL. For more complete information, you should carefully review our amended and restated certificate of incorporation, amended and restated bylaws and the DGCL.

DESCRIPTION OF CAPITAL STOCK

Authorized Capital Stock

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

Common Stock

Holders of shares of our common stock are entitled to one vote for each share held of record on all matters submitted to a vote of stockholders. The holders of a plurality of the shares of our common stock entitled to vote in any election of directors can elect all of the directors standing for election.

Holders of shares of our common stock are entitled to receive dividends when and if declared by our board of directors out of funds legally available therefor, subject to any statutory or contractual restrictions on the payment of dividends and to any restrictions on the payment of dividends imposed by the terms of any outstanding preferred stock.

Upon our dissolution or liquidation or the sale of all or substantially all of our assets, after payment in full of all amounts required to be paid to creditors and to the holders of preferred stock having liquidation preferences, if any, the holders of shares of our common stock will be entitled to receive pro rata our remaining assets available for distribution.

Holders of shares of our common stock do not have preemptive, subscription, redemption or conversion rights.

Preferred Stock

Our amended and restated certificate of incorporation authorizes our board of directors to establish one or more series of preferred stock (including convertible preferred stock). Unless required by law or by any stock exchange, the authorized shares of preferred stock will be available for issuance without further action by our stockholders. Our board of directors is able to determine, with respect to any series of preferred stock, the terms and rights of that series, including:

- the designation of the series;
- the number of shares of the series, which our board may, except where otherwise provided in the preferred stock designation, increase or decrease, but not below the number of shares then outstanding;
- the voting rights, if any, of the holders of the series;
- whether dividends, if any, will be cumulative or non-cumulative and the dividend rate of the series;
- the dates at which dividends, if any, will be payable;
- the rights of priority and amounts payable, if any, on shares of the series in the event of any voluntary or involuntary liquidation, dissolution or winding-up of the affairs of our company;
- the redemption rights and price or prices, if any, for shares of the series;
- the terms of any purchase, retirement or sinking fund, if any, provided for shares of the series;
- the terms, if any, upon which the shares of the series will be convertible into or exchangeable for shares of any other class, classes or series or other securities, whether or not issued by our company or any other entity;
- restrictions, if any, upon issuance of indebtedness of our company so long as any shares of the series are outstanding; and
- restrictions, if any, on the issuance of shares of the same series or of any other class or series.

We could issue a series of preferred stock that could, depending on the terms of the series, impede or discourage an acquisition attempt or other transaction that some, or a majority, of our stockholders might believe to be in their best interests or in which our stockholders might receive a premium for their shares of common stock over the market price of the shares of common stock.

Authorized but Unissued Capital Stock

The DGCL does not require stockholder approval for any issuance of authorized shares. However, the listing requirements of the Nasdaq Global Market, which apply so long as our common stock remains listed on the Nasdaq Global Market, require stockholder approval of certain issuances equal to or exceeding 20% of the then outstanding voting power or then outstanding number of shares of common stock. These additional shares may be used for a variety of corporate purposes, including future public offerings, to raise additional capital or to facilitate acquisitions.

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

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

Undesignated Preferred Stock

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

Requirements for Advance Notification of Stockholder Meetings, Nominations and Proposals

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

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

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

No Cumulative Voting

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

Removal of Directors

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

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

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

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

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

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

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

Stockholder Action by Written Consent

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

Delaware Anti-Takeover Statute

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

- prior to the date of the transaction, the board of directors of the corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder;
- upon completion of the transaction that resulted in the stockholder becoming an interested stockholder, the stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the number of shares outstanding (1) shares owned by persons who are directors and also officers and (2) shares owned under employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or
- on or subsequent to the date of the transaction, the business combination is approved by the board and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least 66 2/3% of the outstanding voting stock which is not owned by the interested stockholder.

Generally, a business combination includes a merger, asset or stock sale, or other transaction resulting in a financial benefit to the interested stockholder. An interested stockholder is a person who, together with affiliates and associates, owns or, within three years prior to the determination of interested stockholder status, did own 15% or more of a corporation's outstanding voting stock. Since Section 203 will apply to us, we expect that it would have an anti-

takeover effect with respect to transactions our board of directors does not approve in advance. In such event, we would also anticipate that Section 203 could discourage attempts that might result in a premium over the market price for the shares of common stock held by stockholders.

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

Choice of Forum

Our amended and restated 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 amended and restated certificate of incorporation or our amended and restated bylaws; and (iv) any action asserting a claim against us that is governed by the internal affairs doctrine. In addition, our amended and restated 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 of 1933, as amended. 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 amended and restated certificate of incorporation and amended and restated bylaws described above. It is possible that a court of law could find the choice of forum provisions contained in our amended and restated certificate of incorporation or amended and restated bylaws to be inapplicable or unenforceable if challenged in a proceeding or otherwise.

Exhibit 10.6

Summary of Non-Employee Director Compensation Policy

Under the Company's non-employee director compensation policy, all non-employee directors will be paid an annual retainer fee of $50,000 and such additional fees as are set forth in the following table. All payments will be made quarterly in arrears.

Non-Employee Director	Annual Fee
Lead Director	$ 35,000
Non-Executive Chair	$ 30,000
Chairman of the audit committee	$ 20,000
Member of the audit committee (other than chairman)	$ 10,000
Chairman of the compensation committee	$ 15,000
Member of the compensation committee (other than chairman)	$ 7,500
Chairman of the governance and nominating committee	$ 10,000
Member of the governance and nominating committee (other than chairman)	$ 5,000

Under the policy, each individual who is initially appointed or elected to the board of directors will be eligible to receive an option to purchase 34,000 shares of our common stock under the 2017 Equity Incentive Plan on the date he or she first becomes a non-employee director. These option grants will vest annually over a three-year period from the date of grant, subject to continued service as a non-employee director through that vesting date. In addition, on the date of the annual meeting of stockholders, each continuing non-employee director who has served on the board of directors for a minimum of six months will be eligible to receive an option grant to purchase 12,000 shares of our common stock and 3,000 restricted stock units, both of which will vest in full upon the earlier of the first anniversary of the date of grant or the date of the next annual meeting of stockholders. The exercise price for each of the option grants will be equal to the fair market value of our common stock on the date of grant. These new director grants and annual grants will be subject to approval by our board of directors at the time of grant. The share numbers set forth herein will be appropriately adjusted for any split or recapitalization of the Company's securities.

June 23, 2020

Joe Shulman
116 Auburn Street
Newton, MA 02466

Dear Joe

Congratulations on your offer of employment with Rhythm Pharmaceuticals (also referred to in this letter as the "Company"). I am confident you will find your career with Rhythm to be filled with opportunities, challenges and rewards. We take great pride in hiring professionals who have talent, drive, creativity and commitment and we are delighted to have you join our team. Below you will find important information about our organization, your individual position, rewards and benefits.

Employment. I am pleased to offer you the position of Senior Vice President, Technical Operations, beginning on July 27, 2020 (the "Start Date"), reporting to Hunter Smith, Interim President & CEO. You will be responsible for performing the duties associated with the position above or as the Company may otherwise assign to you. Your primary place of employment will initially be in the Company's offices located in Boston, Massachusetts; however, you will be expected to travel as may be necessary to fulfill your responsibilities. In the course of your employment with the Company, you will be subject to, and required to comply with, all Company policies and all applicable laws and regulations.

Base Salary. During your employment, your salary will be $375,000 annualized, subject to all required and elected taxes and other withholdings. Your salary may be adjusted from time to time in accordance with normal business practice and in the sole discretion of the Company.

Annual Incentive Bonus. Following the end of each fiscal year and subject to the approval by the Company's Board of Directors in its sole discretion, you will be eligible to earn an incentive bonus, based on your performance and the Company's performance, each during the applicable fiscal year, and subject to your continued employment in good standing on the date of payment of such incentive bonus. Your target annual incentive bonus opportunity shall be 30% of your annualized base salary.

Signing Bonus. The Company will pay you a one-time cash signing bonus of $60,000 at the first regularly scheduled payroll period of the Company which occurs after your Start Date. Voluntary termination (unless following a Change of Control) or termination for cause within the first twenty-four (24) months of employment will require repayment by you of such signing bonus, payable to Rhythm within 90 days of the termination date.

Equity Grant. Subject to and upon the approval of the Board of Directors of the Company after your Start Date, the Company shall grant to you a stock option (the "Option") under the Company's 2017 Equity Incentive Plan, as it may be amended from time to time (the "Plan"), to purchase 85,000 shares (subject to any adjustments for any stock splits, stock dividends, reverse stock splits or recapitalizations that are effected at any time during the period commencing after the date of this offer letter and ending on the grant date of the Option, the "Option Shares") of the Company's common stock, $0.001 par value per share (the "Common Stock"), at an exercise price equal to fair market value of the Common Stock, as determined by

the Board of Directors of the Company, on the date of the grant of the Option (the "Grant Date"). Promptly after the Grant Date, the Company and you shall execute and deliver to each other the Company's then standard form of stock option agreement, evidencing the Option and the terms thereof. The Option shall be subject to, and governed by, the terms and provisions of the Plan and your stock option agreement.

Subject to the terms and conditions set forth below in this letter of employment and unless the Board of Directors of the Company shall otherwise determine on the Grant Date, the Option shall be exercisable for twenty-five percent (25%) of the Option Shares as of the first anniversary of your Start Date, and the remainder of the Option Shares shall become exercisable thereafter in a series of twelve (12) equal quarterly installments until such Option shall have become fully vested and exercisable.

Upon termination of your employment with the Company, you may exercise the Option to the extent then outstanding and exercisable, but only until the earlier to occur of (i) the expiration of the term of the Option and (ii) the expiration of the limited period of time set forth in the Plan and/or your stock option agreement for the exercise of the Option following termination of your employment with the Company.

Any Option Shares you acquire pursuant to the exercise of the Option shall be subject to the terms and restrictions on transfer set forth in the Plan, your stock option agreements and any other agreement to which you shall become, or are required to become, a party pursuant to the terms of the Plan.

You may be awarded additional equity grants from time to time in accordance with normal business practice and in the sole discretion of the Company's Board of Directors. The terms of any future equity grant will be consistent with any plan under which they are granted and the terms of the applicable agreement under which the award(s) are granted.

Benefits. You may participate in any and all benefit programs that the Company establishes and makes available to its employees from time to time, subject to the terms and conditions of those programs. The Company's benefits programs are subject to change at any time in the Company's sole discretion.

Vacation. You will be eligible to annual paid vacation of four (4) weeks, accrued over the course of the year and prorated based on your start date. Your accrual and use of vacation time will be pursuant and subject to any vacation or time off policy the Company may establish or modify from time to time. The Company's vacation policy is subject to change at any time in the Company's sole discretion.

Severance. If the Company terminates your employment without Cause (as defined below) or you resign your employment with the Company for Good Reason (as defined below) (in either event, a "Qualifying Termination"), then, subject to your execution of a release acceptable to the Company (the "Release"), the expiration of any revocation period provided in the Release and your continued compliance with the terms of the NDA (as defined below), the Company will provide severance pay to you in an amount equal to your then-current base salary rate for a period of nine (9) months (the "Regular Severance Amount"). However, if such a Qualifying Termination occurs on or prior to the first anniversary of the Start Date, the Regular Severance Amount will be an amount equal to your then-current base salary rate for a period of twelve (12) months.

If there is a Qualifying Termination within the three (3) months immediately preceding or the twelve (12) months immediately following a Change of Control (as such term is defined in the Plan), then, subject to your execution of a Release following your Separation from Service (as defined below), the expiration of any revocation period provided in the Release and your continued compliance with the terms of the NDA, the Company will, in lieu of the Regular Severance Amount, provide you with severance pay in an amount (the "Change of Control Severance Amount") equal to your then-current base salary rate for a period of twelve (12) months plus an amount equal to 100% of your then-applicable target annual incentive bonus for the fiscal year in which such Qualifying Termination occurs, which then-applicable target annual incentive bonus amount shall be payable by the Company in equal installments during such twelve (12) month period at the same time that the Company is required to make payment of such monthly base salary payments during such twelve (12) month period.

Any severance amount to which you may be entitled under this letter will be paid in substantially equal installments in accordance with the Company's ordinary payroll practices, beginning on the first payroll date following the date that is either (i) sixty (60) days after the date of your Separation from Service, or (ii) in the case of a Separation from Service that is a Qualifying Termination that occurs within the three (3) months immediately preceding a Change of Control, sixty (60) days after the date of such Change of Control, provided that, in the case of either of the foregoing clauses (i) and (ii), the Company, in its sole discretion, may have the option to pay any such severance amount to you as a lump sum. To be eligible for either the Regular Severance Amount or the Change of Control Severance Amount, as applicable, you must execute and deliver the Release to the Company and allow it to become effective within thirty (30) days of your Separation from Service or, if later, within thirty (30) days of a Change of Control giving rise to a Change of Control Severance Amount entitlement.

In addition, if following your Separation from Service, you are eligible for and timely elect continued medical insurance coverage pursuant to COBRA, the Company will reimburse you for the applicable premiums for you and your eligible dependents during the period commencing on the date of your Separation from Service and ending on the earlier to occur of (a) the final day of the applicable severance period and (b) the date you otherwise become ineligible for continued coverage under COBRA. Notwithstanding the foregoing, if the Company determines that it cannot provide such reimbursement of premiums to you without potentially violating applicable law, the Company shall not be obligated to make any such payments or reimbursements to you.

If the Qualifying Termination occurs at any time within the three (3) months immediately preceding or the twelve (12) months immediately following a Change of Control, then each outstanding equity award in the Company held by you (including, without limitation, the Option) shall immediately vest and, if applicable, become exercisable with respect to one hundred percent (100%) of the shares of equity of the Company subject thereto. The foregoing provisions of this paragraph shall apply notwithstanding anything express or implied to the contrary in any agreement or award between you and the Company, or in any plan of the Company, that is applicable to such outstanding equity award.

409A Matters. Notwithstanding anything herein to the contrary, in the event that any compensation or benefit that constitutes "nonqualified deferred compensation" within the meaning of Section 409A of the Internal Revenue Code of 1986, as amended (the "Code"), becomes payable upon the

occurrence of a Change of Control, such compensation or benefit shall not be paid unless such Change of Control constitutes a "change in control event" within the meaning of Section 409A of the Code.

Withholding Taxes. All payments and benefits described in this letter agreement or that you may otherwise be entitled or eligible to receive as a result of your employment with the Company will be subject to applicable federal, state and local tax withholdings.

280G Matters. If any payment or benefit you would receive under this letter, when combined with any other payment or benefit you receive pursuant to the termination of your employment with the Company ("Payment") would (i) constitute a "parachute payment" within the meaning of Section 280G of the Code, and (ii) but for this sentence, be subject to the excise tax imposed by Section 4999 of the Code (the "Excise Tax"), then such Payment shall be either (x) the full amount of such Payment or (y) such lesser amount (with your choice of whether to reduce cash payments or stock option compensation or both) as would result in no portion of the Payment being subject to the Excise Tax, whichever of the foregoing amounts, taking into account the applicable federal, state and local employment taxes, income taxes and the Excise Tax results in your receipt, on an after-tax basis, of the greater amount of the Payment notwithstanding that all or some portion of the Payment may be subject to the Excise Tax.

Definitions

Separation from Service. For purposes of this letter, "Separation from Service" means a "separation from service" within the meaning of Section 409A of the Code. Each installment payment provided under this letter shall at all times be considered a separate and distinct payment for purposes of Section 409A of the Code. Notwithstanding anything in this letter to the contrary, to the extent required to avoid a prohibited distribution under Section 409A of the Code, the benefits provided under this letter will not be provided to you until the earlier of (a) the expiration of the six-month period measured from the date of your Separation from Service with the Company or (b) the date of your death. Upon the first business day after expiration of the relevant period, all payments delayed pursuant to the preceding sentence will be paid in a lump sum and any remaining payments due will be paid as otherwise provided herein.

Cause. "Cause" shall mean the occurrence of any of the following events by the individual: (i) commission of any crime involving the Company, or any crime involving fraud, breach of trust, or physical or emotional harm to any person, moral turpitude or dishonesty; (ii) any unauthorized use or disclosure of the Company's proprietary information (other than any such use or disclosure that is not intentional and is not material); (iii) any intentional misconduct or gross negligence that has a material adverse effect on the Company's business or reputation; (iv) any material breach by you of any agreement between you and the Company that is not cured within thirty (30) days after receipt of written notice from the Company describing any such breach; or (v) repeated and willful failure to perform the duties, functions and responsibilities of the individual's position after a written warning from the Company.

Good Reason. "Good Reason" shall mean your resignation from all positions you then hold with the Company if: (A) without your written consent (i) there is a material diminution in the nature or scope of your responsibilities, duties, authority, or title; (ii) there is a material reduction of your base salary; provided, however, that a material reduction in your base salary pursuant to a salary

reduction program affecting all or substantially all of the employees of the Company and that does not adversely affect you to a greater extent than other similarly situated employees shall not constitute Good Reason; or (iii) you are required to relocate your primary work location to a facility or location that would increase your one way commute distance by more than thirty-five (35) miles from your primary work location as of immediately prior to such change, (B) you provide written notice outlining such conditions, acts or omissions to the Company's Chief Executive Officer, President, or General Counsel within thirty (30) days immediately following such material change or reduction, (C) such material change or reduction is not remedied by the Company within thirty (30) days following the Company's receipt of such written notice and (D) your resignation is effective not later than thirty (30) days after the expiration of such thirty (30) day cure period. "Good Reason" shall also mean your resignation, at your sole discretion, on the one-year anniversary of a Change of Control from all positions you then hold with the Company or its successor if by that date you have not entered into a written letter or agreement with the Company or such successor that provides for your continued employment with the Company or such successor. For purposes of clarification, any Qualifying Termination that occurs on the first anniversary of a Change of Control shall be deemed and treated as occurring within the twelve (12) months immediately following a Change of Control for all purposes of this letter.

Invention, Non-Disclosure, Non-Competition and Non-Solicitation Obligations. At or prior to the Start Date, you shall execute and deliver for the benefit of the Company the Employee Confidentiality, Assignment of Inventions, Non-Competition and Non-Solicitation Agreement in the form attached hereto as Exhibit A.

At-Will Employment. This letter shall not be construed as an agreement, either express or implied, to employ you for any stated term, and shall in no way alter the Company's policy of employment at-will. Similarly, nothing in this letter shall be construed as an agreement, either express or implied, to pay you any compensation or grant you any benefit beyond the end of your employment with the Company, except as otherwise explicitly set forth in this letter. This letter supersedes all prior understandings, whether written or oral, with respect to the subject matter of this letter.

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

Joe, I look forward to working with you as part of the Rhythm team. Please indicate your acceptance of this letter of employment by signing a copy of this offer letter and returning it to us by Monday, June 29, 2020.

Sincerely,
/s/ Hunter Smith
Hunter Smith
Interim President & Chief Executive Officer

The foregoing correctly sets forth the terms of my at-will employment with Rhythm. I am not relying on any representations other than those set forth above.

/s/ Joe Shulman	24JUN2020
Joe Shulman	Date

EXHIBIT A

EXECUTED NDA

[*See attached*]

Exhibit 21.1

Subsidiaries of Rhythm Pharmaceuticals, Inc.

Entity	Jurisdiction of Organization or Incorporation
Rhythm Pharmaceuticals Limited	Ireland
Rhythm Securities Corp.	Massachusetts
Rhythm Pharmaceuticals Netherlands, B.V.	The Netherlands
Rhythm Pharmaceuticals UK Limited	United Kingdom
Rhythm Pharmaceuticals France SAS	France
Rhythm Pharmaceuticals Italy S.r.L.	Italy
Rhythm Pharmaceuticals Canada Inc.	Canada
Rhythm Pharmaceuticals Germany GmbH	Germany
Rhythm Pharmaceuticals Spain S.L.	Spain

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the following Registration Statements:

(1) Registration Statement (Form S-3 No. 333-260689) of Rhythm Pharmaceuticals, Inc.,

(2) Registration Statement (Form S-8 No. 333-263171) pertaining to the 2022 Employment Inducement Plan of Rhythm Pharmaceuticals, Inc.,

(3) Registration Statement (Form S-8 No. 333-263168) pertaining to the 2017 Equity Incentive Plan and the 2017 Employee Stock Purchase Plan of Rhythm Pharmaceuticals, Inc.,

(4) Registration Statement (Form S-8 No. 333-253709) pertaining to the 2017 Equity Incentive Plan of Rhythm Pharmaceuticals, Inc.,

(5) Registration Statement (Form S-8 No. 333-236829) pertaining to the 2017 Equity Incentive Plan and the 2017 Employee Stock Purchase Plan of Rhythm Pharmaceuticals, Inc.,

(6) Registration Statement (Form S-8 No. 333-229642) pertaining to the 2017 Equity Incentive Plan and the 2017 Employee Stock Purchase Plan of Rhythm Pharmaceuticals, Inc.,

(7) Registration Statement (Form S-8 No. 333-223647) pertaining to the 2017 Equity Incentive Plan of Rhythm Pharmaceuticals, Inc., and

(8) Registration Statement (Form S-8 No. 333-220925) pertaining to the 2017 Equity Incentive Plan and the 2017 Employee Stock Purchase Plan of Rhythm Pharmaceuticals, Inc.;

of our report dated March 1, 2023, with respect to the consolidated financial statements of Rhythm Pharmaceuticals, Inc. included in this Annual Report (Form 10-K) of Rhythm Pharmaceuticals, Inc. for the year ended December 31, 2022.

/s/ Ernst & Young LLP

Boston, Massachusetts
March 1, 2023

Exhibit 31.1

CERTIFICATION

I, David P. Meeker M.D., certify that:

1. I have reviewed this annual report on Form 10-K of Rhythm Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 1, 2023

/s/ David P. Meeker M.D.

Name: David P. Meeker M.D.
Title: Chief Executive Officer and President
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION

I, Hunter C. Smith, certify that:

1. I have reviewed this annual report on Form 10-K of Rhythm Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 1, 2023

/s/ Hunter C. Smith
Name: Hunter C. Smith
Title: Chief Financial Officer
(Principal Financial Officer)

Exhibit 32.1

CERTIFICATION OF CHIEF EXECUTIVE OFFICER
PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

I, David P. Meeker M.D., certify pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to my knowledge, this Annual Report on Form 10-K of Rhythm Pharmaceuticals, Inc. for the fiscal year ended December 31, 2022 fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934 and the information contained in such Form 10-K fairly presents, in all material respects, the financial condition and results of operations of Rhythm Pharmaceuticals, Inc.

/s/ David P. Meeker M.D.
Name: David P. Meeker M.D.
Title: Chief Executive Officer and President
(Principal Executive Officer)

March 1, 2023

Exhibit 32.2

CERTIFICATION OF CHIEF FINANCIAL OFFICER
PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

I, Hunter C. Smith, certify pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to my knowledge, this Annual Report on Form 10-K of Rhythm Pharmaceuticals, Inc. for the fiscal year ended December 31, 2022 fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934 and the information contained in such Form 10-K fairly presents, in all material respects, the financial condition and results of operations of Rhythm Pharmaceuticals Inc.

/s/ Hunter C. Smith
Name: Hunter C. Smith
Title: Chief Financial Officer
(Principal Financial Officer)

March 1, 2023