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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-Q

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

For the quarterly period ended September 30, 2021
OR

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

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

RHYTHM PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

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

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

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

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

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

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

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 is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒.

The number of shares outstanding of the registrant's Common Stock as of October 26, 2021 was 50,268,312.

RHYTHM PHARMACEUTICALS, INC.

FORM 10-Q

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PART I – FINANCIAL INFORMATION

Item 1. Financial Statements

Rhythm Pharmaceuticals, Inc.

Condensed Consolidated Balance Sheets

(in thousands, except share and per share data)

(Unaudited)

	September 30, 2021	December 31, 2020
Assets		
Current assets:		
Cash and cash equivalents	$ 92,372	$ 100,854
Short-term investments	235,982	71,938
Prepaid expenses and other current assets	7,282	8,876
Total current assets	335,636	181,668
Property and equipment, net	2,956	3,195
Right-of-use asset	1,598	1,807
Intangible assets, net	4,772	—
Restricted cash	328	403
Other long-term assets	10,533	—
Total assets	$ 355,823	$ 187,073
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 4,614	$ 4,900
Accrued expenses and other current liabilities	18,265	12,559
Lease liability	588	535
Total current liabilities	23,467	17,994
Long-term liabilities:		
Deferred tax liability	7,989	—
Lease liability	2,104	2,551
Total liabilities	33,560	20,545
Commitments and contingencies (Note 5)		
Stockholders' equity:		
Preferred Stock, $0.001 par value: 10,000,000 shares authorized; no shares issued and outstanding at September 30, 2021 and December 31, 2020	—	—
Common stock, $0.001 par value: 120,000,000 shares authorized; 50,268,312 and 44,235,903 shares issued and outstanding September 30, 2021 and December 31, 2020, respectively	50	44
Additional paid-in capital	808,265	625,762
Accumulated other comprehensive income	21	49
Accumulated deficit	(486,073)	(459,327)
Total stockholders' equity	322,263	166,528
Total liabilities and stockholders' equity	$ 355,823	$ 187,073

The accompanying notes are an integral part of these unaudited condensed consolidated financial statements

Rhythm Pharmaceuticals, Inc.

Condensed Consolidated Statements of Operations and Comprehensive Loss

(in thousands, except share and per share data)

(Unaudited)

	Three months ended September 30,		Nine months ended September 30,	
	2021	2020	2021	2020
Product revenue, net	$ 1,028	$ —	$ 1,337	$ —
Costs and expenses:				
Cost of sales	222	—	363	—
Research and development	27,539	22,995	72,554	68,496
Selling, general, and administrative	17,507	11,289	47,490	33,006
Total costs and expenses	45,268	34,284	120,407	101,502
Loss from operations	(44,240)	(34,284)	(119,070)	(101,502)
Other income:				
Other income	—	—	100,000	—
Interest income, net	138	466	313	2,403
Total other income, net	138	466	100,313	2,403
Loss before taxes	(44,102)	(33,818)	(18,757)	(99,099)
Provision for (benefit from) income taxes	(8,995)	—	7,989	—
Net loss	$ (35,107)	$ (33,818)	$ (26,746)	$ (99,099)
Net loss per share, basic and diluted	$ (0.70)	$ (0.77)	$ (0.54)	$ (2.25)
Weighted-average common shares outstanding, basic and diluted	50,246,303	44,142,334	49,374,336	44,097,178
Other comprehensive loss:				
Net loss	$ (35,107)	$ (33,818)	$ (26,746)	$ (99,099)
Unrealized (loss) gain on marketable securities	—	(392)	(107)	238
Comprehensive loss	$ (35,107)	$ (34,210)	$ (26,853)	$ (98,861)

The accompanying notes are an integral part of these unaudited condensed consolidated financial statements

Rhythm Pharmaceuticals, Inc.

Condensed Consolidated Statements of Stockholders' Equity

(in thousands, except share data)

(Unaudited)

	Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balance at December 31, 2020	44,235,903	$ 44	$ 625,762	$ 49	$ (459,327)	$ 166,528
Stock compensation expense	—	—	5,191	—	—	5,191
Issuance of common stock in connection with ESPP	17,000	—	388	—	—	388
Issuance of common stock in connection with exercise of stock options and vesting of restricted stock units	198,855	—	3,466	—	—	3,466
Issuance of common stock upon completion of public offering, net of offering costs	5,750,000	6	161,725	—	—	161,731
Unrealized loss on marketable securities	—	—	—	(107)	—	(107)
Net income	—	—	—	—	43,750	43,750
Balance at March 31, 2021	50,201,758	50	796,532	(58)	(415,577)	380,947
Stock compensation expense	—	—	5,669	—	—	5,669
Issuance of common stock in connection with exercise of stock options	24,981	—	383	—	—	383
Unrealized gain on marketable securities	—	—	—	79	—	79
Net loss	—	—	—	—	(35,389)	(35,389)
Balance at June 30, 2021	50,226,739	50	802,584	21	(450,966)	351,689
Stock compensation expense	—	—	5,268	—	—	5,268
Issuance of common stock in connection with ESPP	21,051		233			233
Issuance of common stock in connection with exercise of stock options	20,522	—	180	—	—	180
Unrealized gain on marketable securities	—	—	—	—	—	—
Net loss	—	—	—	—	(35,107)	(35,107)
Balance at September 30, 2021	50,268,312	$ 50	$ 808,265	$ 21	$ (486,073)	$ 322,263
Balance at December 31, 2019	43,996,753	$ 44	$ 606,307	$ —	$ (325,331)	$ 281,020
Stock compensation expense	—	—	5,475	—	—	5,475
Issuance of common stock in connection with ESPP	18,673	—	324	—	—	324
Issuance of common stock in connection with exercise of stock options	72,964	—	383	—	—	383
Unrealized gain on marketable securities	—	—	—	63	—	63
Net loss	—	—	—	—	(34,164)	(34,164)
Balance at March 31, 2020	44,088,390	44	612,489	63	(359,495)	253,101
Stock compensation expense	—	—	3,028	—	—	3,028
Issuance of common stock in connection with exercise of stock options	27,222	—	174	—	—	174
Unrealized gain on marketable securities	—	—	—	567	—	567
Net loss	—	—	—	—	(31,117)	(31,117)
Balance at June 30, 2020	44,115,612	44	615,691	630	(390,612)	225,753
Stock compensation expense		—	4,695	—	—	4,695
Issuance of common stock in connection with ESPP	11,379	—	198	—	—	198
Issuance of common stock in connection with exercise of stock options	77,754	—	501	—	—	501
Unrealized loss on marketable securities	—	—	—	(392)	—	(392)
Net loss	—	—	—	—	(33,818)	(33,818)
Balance at September 30, 2020	44,204,745	$ 44	$ 621,085	$ 238	$ (424,430)	$ 196,937

The accompanying notes are an integral part of these unaudited condensed consolidated financial statements

Rhythm Pharmaceuticals, Inc.

Condensed Consolidated Statements of Cash Flows

(in thousands)

(Unaudited)

	Nine months ended September 30, 2021	2020
Operating activities		
Net loss	$ (26,746)	$ (99,100)
Adjustments to reconcile net loss to cash used in operating activities:		
Stock-based compensation expense	16,128	13,198
Gain on sale of priority review voucher	(100,000)	—
Deferred tax provision	7,989	—
Depreciation and amortization	833	512
Non-cash rent expense	(185)	(173)
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	1,591	1,092
Other long-term assets	(10,533)	—
Accounts payable, accrued expenses and other current liabilities	5,392	(8,387)
Net cash used in operating activities	(105,531)	(92,858)
Investing activities		
Purchases of short-term investments	(456,238)	(53,398)
Maturities of short-term investments	292,197	150,172
Proceeds from sale of priority review voucher	100,000	—
Milestone obligation under license agreement	(5,000)	
Purchases of property and equipment	(366)	(130)
Net cash (used in) provided by investing activities	(69,407)	96,644
Financing activities		
Net proceeds from issuance of common stock	161,731	—
Proceeds from the exercise of stock options	4,029	1,067
Proceeds from issuance of common stock from ESPP	621	522
Net cash provided by financing activities	166,381	1,589
Net (decrease) increase in cash, cash equivalents and restricted cash	(8,557)	5,375
Cash, cash equivalents and restricted cash at beginning of period	101,257	62,697
Cash, cash equivalents and restricted cash at end of period	$ 92,700	$ 68,072

The accompanying notes are an integral part of these unaudited condensed consolidated financial statements

Rhythm Pharmaceuticals, Inc.

Notes to Unaudited Condensed Consolidated Financial Statements

(In thousands, except share and per share information)

1. Nature of Business

Rhythm Pharmaceuticals, Inc. (the "Company" or "we") is a commercial-stage biopharmaceutical company focused on changing the paradigm for the treatment of rare genetic diseases of obesity, which are characterized by early-onset, severe obesity and an insatiable hunger or hyperphagia. Our lead product candidate is IMCIVREE® (setmelanotide), a potent melanocortin-4 receptor, or MC4R, agonist for the treatment of rare genetic diseases of obesity. We believe IMCIVREE, for which we have exclusive worldwide rights, has the potential to restore dysfunctional MC4R signaling due to impaired MC4R pathway function. MC4R pathway deficiencies result in the disruption of satiety signals and energy homeostasis in the body, which, in turn, leads to intense feelings of hunger and to obesity. IMCIVREE has been approved by the U.S. Food and Drug Administration, or FDA, for chronic weight management in adult and pediatric patients six years of age and older with obesity due to proopiomelanocortin, or POMC, proprotein convertase subtilisin/kexin type 1, or PCSK1, or leptin receptor, or LEPR, deficiency confirmed by genetic testing. IMCIVREE also has been approved by the European Commission for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. IMCIVREE is now commercially available in the United States, and we are pursuing an international strategy to establish access and reimbursement for IMCIVREE in the European Union, or EU, and Great Britain. We also have completed and submitted a supplemental New Drug Application, or sNDA, to the U.S. Food and Drug Administration or FDA, and a Type II variation marketing authorization application, or MAA, to the EMA for IMCIVREE for the treatment of obesity and control of hunger in adult and pediatric patients 6 years of age and older with Bardet-Biedl syndrome, or BBS, or Alström syndrome.

The Company is a Delaware corporation organized in February 2013 under the name Rhythm Metabolic, Inc., and as of October 2015, under the name Rhythm Pharmaceuticals, Inc.

The Company's continued development efforts are focused on obesity related to several single gene-related, or monogenic, MC4R pathway deficiencies: Bardet-Biedl and Alstrom syndromes; obesity due to a genetic variant in one of the two alleles of the POMC, PCSK1 or LEPR gene, or heterozygous POMC, PCSK1 or LEPR obesity (collectively HETs); obesity due to steroid receptor coactivator 1, or SRC1, deficiency; obesity due to SH2B adapter protein 1, or SH2B1, deficiency; hypothalamic obesity; and MC4R deficiency obesity. In addition, we have expanded our development program to explore setmelotide's potential efficacy in patients with severe obesity which may be due to variants in an additional 31 genes that are related to the MC4R pathway. There are additional diseases being studied as part of investigator-initiated protocols. Currently, there are no effective or approved treatments for these MC4R pathway-related diseases. The Company believes that the MC4R pathway is a compelling target for treating these genetic diseases because of its critical role in regulating appetite and weight by promoting satiety and weight control, and that peptide therapeutics are uniquely suited for activating this target.

The Company is subject to risks and uncertainties common to commercial-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.

Liquidity

The Company has incurred operating losses and negative cash flows from operations since inception. As of September 30, 2021, the Company had an accumulated deficit of $486,073. The Company has primarily funded these losses through the proceeds from the sales of common and preferred stock, asset sales as well as capital contributions received from the former parent company, Rhythm Holdings LLC. To date, the Company has minimal product revenue and management expects operating losses to continue for the foreseeable future. The Company has devoted substantially all of its resources to its drug development efforts, comprising of research and development, manufacturing, conducting clinical trials for its product candidates, protecting its intellectual property, pre-commercialization activities and general and administrative functions relating to these operations. The future success of the Company is dependent on its ability to develop its product candidates and ultimately upon its ability to attain profitable operations.

In February 2021, the Company completed the sale of a Rare Pediatric Disease Priority Review Voucher, or PRV, that it received in connection with the approval of IMCIVREE for $100,000. As the PRV did not have a carrying value, the gain recognized within Other income (loss) was equal to the gross proceeds received, with costs related to the sale of the voucher recorded within selling, general and administrative expenses.

At September 30, 2021, the Company had $328,354 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, 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 into at least the second half of 2023.

2. Summary of Significant Accounting Policies

Basis of Presentation

The Company's unaudited condensed consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States, or GAAP, and the applicable rules and regulations of the Securities and Exchange Commission, or SEC, regarding interim financial reporting. 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, or ASC, and Accounting Standards Updates, or ASU, of the Financial Accounting Standards Board, or FASB. As permitted under these rules, certain footnotes or other financial information that are normally required by GAAP have been condensed or omitted.

The accompanying interim balance sheet as of September 30, 2021, the statements of operations and comprehensive income (loss) for the three and nine months ended September 30, 2021 and 2020, the statements of stockholders equity for the three and nine months ended September 30, 2021 and 2020 and the statements of cash flows for the nine months ended September 30, 2021 and 2020 and the related footnote disclosures are unaudited. In management's opinion, the unaudited interim financial statements have been prepared on the same basis as the audited financial statements as of and for the year ended December 31, 2020 and include all adjustments, which are all normal recurring adjustments, necessary for the fair presentation of the interim financial statements. The results for the nine months ended September 30, 2021 are not necessarily indicative of the results expected for the full fiscal year, any other interim periods, or any future year or period.

The accompanying unaudited condensed consolidated financial statements reflect the application of certain significant accounting policies as described below and elsewhere in these notes to the unaudited condensed consolidated financial statements. As of September 30, 2021, there have been no material changes in the Company's significant accounting policies from those that were disclosed in the Company’s Annual Report on Form 10-K for the year ended December 31, 2020.

Certain amounts totaling $63 in the consolidated statement of stockholders' equity for the three months ended March 31, 2020, related to unrealized gains on marketable securities, have been reclassified from additional paid-in capital to accumulated other comprehensive income to conform to the current period presentation. This reclassification had no impact on the previously reported results of operations or cash flows for the three months ended March 31, 2020.

Risks and Uncertainties

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 nine months ended September 30, 2021, the Company is unable to predict the impact that COVID-19 will have on its financial position and operating results in future periods due to numerous uncertainties. The Company will continue to assess the evolving impact of the COVID-19 pandemic and will make adjustments to its operations as necessary.

Use of Estimates

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent liabilities at the date of the financial statements and the reported amounts of revenue and expenses during the reporting period. The Company bases its estimates on historical experience and other market-specific or other relevant assumptions that it believes to be reasonable under the circumstances. This process may result in actual results differing materially from those estimated amounts used in the preparation of the financial statements if these results differ from historical experience, or other assumptions do not turn out to be substantially accurate, even if such assumptions are reasonable when made. Significant estimates relied upon in preparing these financial statements include accruals related to research and development expenses, assumptions used to record stock-based compensation expense and the valuation allowance on the Company's deferred tax assets. Estimates are periodically reviewed in light of changes in circumstances, facts and experience. Changes in estimates are recorded in the period in which they become known. Actual results could differ materially from those estimates.

Principles of Consolidation

The consolidated financial statements include the accounts of Rhythm Pharmaceuticals, Inc. and its wholly-owned subsidiaries. All significant intercompany balances and transactions have been eliminated in consolidation.

Off-Balance Sheet Risk and Concentrations of Credit Risk

Financial instruments, which potentially subject the Company to significant concentration of credit risk, consist primarily of cash and cash equivalents and short-term investments, which are maintained at two federally insured financial institutions. The deposits held at these two institutions are in excess of federally insured limits. The Company has not experienced any losses in such accounts and management believes that the Company is not exposed to significant credit risk due to the financial position of the depository institutions in which those deposits are held. The Company has no off-balance sheet risk, such as foreign exchange contracts, option contracts, or other foreign hedging arrangements.

Segment Information

Operating segments are defined as components of an entity about which separate discrete information is available for evaluation by the chief operating decision maker, or decision-making group, in deciding how to allocate resources and in assessing performance. The Company 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.

Revenue Recognition

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

Product Revenue, Net

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

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

Reserves for Variable Consideration

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

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

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

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

Trade discounts and allowances: The Company provides customary invoice discounts on IMCIVREE sales to our U.S. customer for prompt payment that are recorded as a reduction of revenue in the period the related product revenue is recognized. In addition, we receive and pay for various distribution services from our customer in the distribution channel. For services that are either not distinct from the sale of our product or for which we cannot reasonably estimate the fair value, such fees are classified as a reduction of product revenue.

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

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

During the three and nine months ended September 30, 2021, we recorded product revenue, net, of $1,028 and $1,337. The table that summarizes balances and activity in each of the product revenue allowance and reserve categories has not been included for the three and nine months ended September 30, 2021 due to the immateriality of the revenue recognized during the periods.

Cost of Product Sales

Prior to receiving approval from the FDA in November 2020 to sell IMCIVREE in the United States, the Company expensed all costs incurred related to the manufacture of IMCIVREE as research and development expense because of the inherent risks associated with the development of a drug candidate, the uncertainty about the regulatory approval process and the lack of history for the Company of regulatory approval of drug candidates. Subsequent to receiving FDA approval in November 2020, the Company has capitalized a nominal amount of inventory related costs that were incurred subsequent to FDA approval. At September 30, 2021, the Company had $95 of inventory recorded as a component of other current assets on the condensed consolidated balance sheet.

Cost of product sales will consist 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 period costs related to certain manufacturing services and inventory adjustment charges. The Company is currently evaluating the impact of this previously expensed inventory on the future cost of product sales.

Accounts Receivable, Net

In general, accounts receivable consists of amounts due from customers, net of customer allowances for cash discounts and chargebacks. The Company's contracts with customers have standard payment terms that generally require payment within 45 days. The Company analyzes accounts that are past due for collectability, and periodically evaluates the creditworthiness of its customers. As of September 30, 2021, we determined an allowance for doubtful accounts was not required based upon our review of contractual payment terms and individual customer circumstances.

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 income (loss).

Intangible assets are evaluated for impairment at least annually in the fourth quarter or more frequently if impairment indicators exist. Events that could result in an impairment, or trigger an interim impairment assessment, include the decision to discontinue the development of a drug, the receipt of additional clinical or nonclinical data regarding our drug candidate or a potentially competitive drug candidate, changes in the clinical development program for a drug candidate, or new information regarding potential sales for the drug. In connection with any impairment assessment, the fair value of the intangible assets as of the date of assessment is compared to the carrying value of the intangible asset. Impairment losses are recognized if the carrying value of an intangible asset is both not recoverable and exceeds its fair value.

Fair Value Measurements

Fair value is the price that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. Financial assets and liabilities carried at fair value are classified and disclosed in one of the following three categories:

Level 1 — Quoted market prices in active markets for identical assets or liabilities.

Level 2 — Observable inputs other than Level 1 prices, such as quoted prices for similar assets or liabilities; quoted prices in markets that are not active; or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities.

Level 3 — Unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities.

The Company's cash equivalents and marketable securities at September 30, 2021 and December 31, 2020 were carried at fair value, determined according to the fair value hierarchy. See Note 4 for further discussion.

The carrying amounts reflected in the consolidated balance sheets for accounts payable and accrued expenses approximate their fair values due to their short-term maturities at September 30, 2021 and December 31, 2020, respectively.

Net Loss Per Share

Basic net loss per share is computed by dividing the net loss by the weighted average number of common shares outstanding during the period, without consideration of potential dilutive securities. Diluted net loss per common share is computed by adjusting the weighted average shares outstanding for the potential dilutive effects of common stock equivalents outstanding during the period calculated in accordance with the treasury stock method. For purposes of the diluted net loss per share calculation, stock options and restricted stock units are considered to be common stock equivalents but have been excluded from the calculation of diluted net loss per share, as their effect would be anti-dilutive

for all periods presented due to the net losses incurred. 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:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
Stock options	5,966,664	5,096,252	5,966,664	5,096,252
Restricted stock units	439,957	179,662	439,957	179,662
Potential common shares	6,406,621	5,275,914	6,406,621	5,275,914

Subsequent Events

The Company considers events or transactions that occur after the balance sheet date but prior to the issuance of the financial statements to provide additional evidence for certain estimates or to identify matters that require additional disclosure. Subsequent events have been evaluated as required.

Application of New or Revised Accounting Standards

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

In June 2016, the FASB issued ASU 2016-13, *Financial Instruments-Credit Losses-Measurement of Credit Losses on Financial Instruments*, which has been subsequently amended by ASU No. 2018-19, ASU No. 2019-04, ASU No. 2019-05, ASU No. 2019-10, ASU No. 2019-11 and ASU No. 2020-03, or ASU 2016-13. The provisions of ASU 2016-13 modify the impairment model to utilize an expected loss methodology in place of the currently used incurred loss methodology and require a consideration of a broader range of reasonable and supportable information to inform credit loss estimates. Since the Company ceased to be an emerging growth company as of December 31, 2020, the Company adopted the standard during the fourth quarter of 2020 and applied the modified retrospective method of adoption to the Company's financial statements as of January 1, 2020. Based on the composition of the investment portfolio as of the adoption date, the adoption of this standard did not have a material impact on the Company's financial position, results of operations and cash flows for the year ended December 31 2020 and no adjustment was required to be recorded to the opening retained earnings balance as of January 1, 2020.

In December 2019, the FASB issued ASU 2019-12, *Income Taxes-Simplifying the Accounting for Income Taxes*, or ASU 2019-12. ASU 2019-12 eliminates certain exceptions related to the approach for intraperiod tax allocation, the methodology for calculating income taxes in an interim period and the recognition of deferred tax liabilities for outside basis differences. The new guidance also simplifies aspects of the accounting for franchise taxes and enacted changes in tax laws or rates and clarifies the accounting for transactions that result in a step-up in the tax basis of goodwill. The standard is effective for annual periods beginning after December 15, 2020 and interim periods within, with early adoption permitted. Adoption of the standard requires certain changes to be made prospectively, with some changes to be made retrospectively. We have adopted ASU 2019-12 as of January 1, 2021 and the adoption of this standard did not have a material impact on the Company's financial position, results of operations and cash flows.

3. Accrued Expenses

Accrued expenses consisted of the following:

	September 30, 2021	December 31, 2020
Research and development costs	$ 8,943	$ 5,815
Professional fees	2,560	648
Payroll related	6,008	5,916
Other	754	180
Accrued expenses	$ 18,265	$ 12,559

4. Fair Value of Financial Assets

As of September 30, 2021 and December 31, 2020, the carrying amount of cash and cash equivalents and short-term investments was $328,354 and $172,792, respectively, which approximates fair value. Cash and cash equivalents and short-term investments includes investments in U.S. treasury securities and money market funds that invest in U.S. government securities that are valued using quoted market prices. Accordingly, money market funds and government funds are categorized as Level 1. The financial assets valued based on Level 2 inputs consist of corporate debt securities and commercial paper, which consist of investments in highly-rated investment-grade corporations.

The following tables present information about the Company's financial assets measured at fair value on a recurring basis and indicate the level of the fair value hierarchy utilized to determine such fair values:

	Fair value Measurements as of September 30, 2021 using:			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash Equivalents:				
Commercial Paper	$ —	$ 38,993	$ —	$ 38,993
Money Market Funds	39,929	—	—	39,929
Marketable Securities:				
Corporate Debt Securities and Commercial Paper	—	235,982	—	235,982
Total	$ 39,929	$ 274,975	$ —	$ 314,904

	Fair value Measurements as of December 31, 2020 using:			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash Equivalents:				
Corporate Debt Securities and Commercial Paper	$ —	$ 36,242	$ —	$ 36,242
Money Market Funds	63,182	—	—	63,182
Marketable Securities:				
Corporate Debt Securities and Commercial Paper	—	71,938	—	71,938
Total	$ 63,182	$ 108,180	$ —	$ 171,362

Marketable Securities

The following tables summarize the Company's marketable securities:

	September 30, 2021			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Assets				
Corporate debt securities and commercial paper (due within 1 year)	$ 235,961	$ 29	$ (8)	$ 235,982
	$ 235,961	$ 29	$ (8)	$ 235,982

	December 31, 2020			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Assets				
Corporate debt securities and commercial paper (due within 1 year)	$ 71,895	$ 43	$ —	$ 71,938
	$ 71,895	$ 43	$ —	$ 71,938

5. Right Of Use Asset and Lease Liability

The Company has a material operating lease for its head office facility and other immaterial operating leases for certain equipment. The Company's office lease has a remaining lease term of 3.8 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 September 30, 2021, the Company has not entered into any lease arrangements classified as a finance lease.

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. The Company has not included the five-year renewal option to extend the lease in its measurement of the ROU asset or lease liability.

The following table presents the maturities of the Company's operating lease liability related to office space as of September 30, 2021, all of which is under a non-cancellable operating lease:

	Operating Lease
Remainder of 2021	$ 203
2022	818
2023	834
2024	851
2025	502
Thereafter	—
Total operating lease payments	3,208
Less: imputed interest	516
Total operating lease liability	$ 2,692

6. Intangible Assets, Net

As of September 30, 2021, the Company's finite-lived intangible assets, which totaled $4,772, 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.

2021	$	114
2022		455
2023		455
2024		455
2025		455
Thereafter		2,838
Total	$	4,772

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 $114 and $228 for the three and nine months ended September 30, 2021. Amortization expense will be included in cost of sales on the consolidated statements of operations and comprehensive loss.

7. Income Taxes

The Company recorded a tax (benefit) of ($8,995) for the three month period ended September 30, 2021. The Company recorded a tax provision of $7,989 for the nine months period ended September 30, 2021 primarily related to the sale of the PRV, offset by a tax benefit from ordinary losses generated by the Company over the remainder of current year. The Company expects to have sufficient tax losses in the current year to offset the income from the sale and thus no current year liability is expected. The Company expects to maintain a full valuation allowance against its net deferred tax assets for the year.

8. Common Stock

On February 9, 2021 the Company completed a public offering of 5,750,000 shares of common stock at an offering price of $30.00 per share, which included the exercise in full by the underwriters of their option to purchase up to 750,000 additional shares of common stock. The Company received $161,731 in net proceeds after deducting underwriting discounts, commissions and offering expenses.

During the three months ended March 31, 2020, the Company entered into a separation agreement with its former Chief Executive Officer, Keith Gottesdiener, M.D. The Company modified certain equity awards held by Dr. Gottesdiener. The modification included the continuation of vesting of stock options through the end of December 31, 2020 and an extension of the post-termination exercise period for vested options from 90 days to up to two years. In connection with this modification, the Company recorded an incremental compensation charge of $2,811 during the nine months ended September 30, 2020.

As of September 30, 2021, an aggregate of 9,972,556 shares of common stock were reserved for future issuance under the Company's stock plans, including outstanding stock options and restricted stock units that have been issued of 6,406,621 shares of common stock and 962,942 shares are available for future grants under the Company's 2017 Employee Stock Purchase Plan.

9. Related-Party Transactions

Expenses paid directly to consultants and vendors considered to be related parties amounted to $450, $808, $1,547, and $2,584 for the three and nine months ended September 30, 2021 and 2020, respectively. Outstanding payments due to these related parties as of September 30, 2021 and December 31, 2020 were $0 and $187, respectively, and were included within accounts payable on the balance sheet.

Item 2. 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 unaudited condensed consolidated financial statements and related notes appearing elsewhere in this Quarterly Report on Form 10-Q. In addition to historical information, some of the information contained in this discussion and analysis or set forth elsewhere in this Quarterly Report on Form 10-Q contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, and is subject to the "safe harbor" created by those sections. All statements other than statements of historical facts contained in this Quarterly Report on Form 10-Q, including without limitation statements regarding: our financial performance, including our expectations regarding our existing cash, operating losses, expenses and sources of future financing; our ability to hire and retain necessary personnel; patient enrollments and the timing thereof; the timing of announcements regarding results of clinical trials; our ability to protect our intellectual property; ongoing activities under and our ability to negotiate our collaboration and license agreements, if needed; our marketing, commercial sales, and revenue generation; expectations surrounding our manufacturing arrangements; the impact of the novel coronavirus, or COVID-19, pandemic on our business and operations and our future financial results; and other statements identified by words 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 are forward-looking statements. These forward-looking statements are neither promises nor guarantees of future performance, and are subject to a variety of known and unknown risks and uncertainties, many of which are beyond our control, and other important factors which could cause actual results to differ materially from those contemplated in such forward-looking statements. We discuss factors that we believe could cause or contribute to these differences below and elsewhere in this report, including but not limited to those set forth in Part II, Item 1A under the heading "Risk Factors" of this Quarterly Report on Form 10-Q. 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 Quarterly Report on Form 10-Q. We caution readers not to place undue reliance upon any such forward-looking statements, which speak only as of the date made.

Overview

We are a commercial-stage biopharmaceutical company focused on changing the paradigm for the treatment of rare genetic diseases of obesity, which are characterized by early-onset, severe obesity and an insatiable hunger or hyperphagia. Our lead product candidate is IMCIVREE® (setmelanotide), a potent melanocortin-4 receptor, or MC4R, agonist for the treatment of rare genetic diseases of obesity. We believe IMCIVREE, for which we have exclusive worldwide rights, has the potential to restore dysfunctional MC4R signaling due to impaired MC4R pathway function. MC4R pathway deficiencies result in the disruption of satiety signals and energy homeostasis in the body, which, in turn, leads to intense feelings of hunger and to obesity. We believe that the MC4R pathway is a compelling target for treating these genetic diseases because of its critical role in regulating appetite and weight by promoting satiety and weight control, and that peptide therapeutics are uniquely suited for activating this target.

IMCIVREE has been approved by the U.S. Food and Drug Administration, or FDA, for chronic weight management in adult and pediatric patients six years of age and older with obesity due to proopiomelanocortin, or POMC, proprotein convertase subtilisin/kexin type 1, or PCSK1, leptin receptor, or LEPR, deficiency confirmed by genetic testing. IMCIVREE became commercially available in the U.S. in the first quarter 2021. The European Commission and Great Britain's Medicines & Healthcare Products Regulatory Agency, or MHRA, in July and September 2021, respectively, granted marketing authorization to IMCIVREE for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. We are making steady progress towards achieving market access in Germany, Great Britain, France, Italy and Spain. Reimbursement dossiers have been submitted in The Netherlands and Israel, and we have recently initiated dossier development in Sweden.

We recently completed and submitted a supplemental New Drug Application, or sNDA, to the U.S. Food and Drug Administration, or FDA, and a Type II variation application to the EMA for IMCIVREE for the treatment of obesity and control of hunger in adult and pediatric patients 6 years of age and older with Bardet-Biedl syndrome, or BBS, or

Alström syndrome. These regulatory submissions were based on data from a pivotal Phase 3 clinical trial evaluating setmelanotide for the treatment of insatiable hunger and severe obesity in individuals with BBS, or Alström syndrome. The trial met its primary and all key secondary endpoints, showing statistically significant and clinically meaningful reductions in weight and hunger scores. All patients who met the primary endpoint defined as more than 10 percent weight loss had BBS and none had Alström syndrome. However, data from this trial, supported by results from the Phase 2 trial, suggest that treatment with setmelanotide may result in decreased weight and hunger in people living with Alström syndrome. Based on FDA timelines, we will know in November 2021 if our sNDA has been accepted with Priority Review, as we have requested. If granted, the FDA typically has a review period of six-months from the date of acceptance. We currently anticipate a commercial launch in the United States in mid-2022. The review timeline in Europe is calendar-based, and we would expect a decision from the European Commission in the second half of 2022.

Our continued development efforts are focused on obesity related to several single gene-related, or monogenic, MC4R pathway deficiencies: obesity due to a heterozygous 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, deficiency; obesity due to SH2B adapter protein 1, or SH2B1, deficiency; hypothalamic obesity; and MC4R deficiency obesity. On January 26, 2021, we announced new interim data from our ongoing Phase 2 Basket Study across individuals with HET obesity and SRC1 and SH2B1 deficiency obesities that we believe demonstrate proof of concept in these diseases. The primary endpoint of the study was the percent of patients in each subgroup showing at least a 5 percent loss of body weight over three months. Consistent with prior clinical experience, setmelanotide was generally well tolerated in each of these rare genetic diseases of obesity. In August 2021, we announced agreement with the FDA and EMA on the clinical design and primary endpoint of our pivotal Phase 3 EMANATE trial of setmelanotide. The trial will be a randomized, double-blind, placebo-controlled study with five independent sub-studies evaluating setmelanotide in patients with: heterozygous POMC/PCSK1 obesity; heterozygous LEPR obesity; certain variants of the SRC1; certain variants of SH2B1 genes; or PCSK1 N221D deletions within the MC4R pathway. Each sub-study will be independent of the others and, if successful, is designed to allow us to submit separate regulatory submissions to the FDA and EMA. We plan to initiate the EMANATE trial in the fourth quarter of 2021 or the first quarter of 2022.

We also recently announced plans to initiate the Phase 2 DAYBREAK trial of setmelanotide in the fourth quarter of 2021. This trial will be a two-stage, double-blind, placebo-controlled study in patients with specific variants within one of 31 genes within the MC4R pathway. We leveraged our proprietary gene curation and selection strategy, which is designed to evaluate a gene's relevance to the MC4R pathway with the goal of identifying genetic patient populations with the potential to benefit from setmelanotide therapy, to identify an additional 31 MC4R pathway genes with strong or very strong pathway relevance.

We also plan to initiate in the fourth quarter of 2021, a Phase 3 randomized, double-blind trial in patients currently on daily setmelanotide therapy ("*switch study*") to evaluate the efficacy of daily and weekly formulations of setmelanotide in patients with obesity due to BBS. In the first half of 2022, we also plan to initate a Phase 3, randomized, double-blind trial in patients naïve to setmelanotide therapy ("*de novo study*") to evaluate the weekly formulation of setmelanotide in patients with BBS. In the first half of 2022, we plan to announce new top-line data from the ongoing exploratory Phase 2 Basket Study evaluating setmelanotide in patients with obesity due to a variant in the MC4 receptor. Additionally, as an FDA post-marketing requirement, we are currently evaluating the effects of setmelanotide on the QT corrected for heart rate, or QTc interval, in healthy volunteers.

We are studying additional diseases as part of investigator-initiated protocols. There are currently no effective or approved treatments for these MC4R pathway-related diseases. The FDA has acknowledged the importance of these results by giving setmelanotide Breakthrough Therapy designation for the treatment of obesity associated with genetic defects upstream of the MC4R in the leptin melanocortin pathways. The Breakthrough Therapy designation currently covers indications for POMC deficiency obesity, LEPR deficiency obesity, BBS and Alström syndrome.

Additional recent clinical, regulatory and corporate updates include:

- In November 2021, at The Obesity Society's ObesityWeek®, a virtual conference, we delivered multiple data presentations including: the first-ever health-related quality of life (HRQOL) data from patients with BBS

treated with setmelanotide; efficacy and safety data from our Phase 3 trial of setmelanotide in BBS and Alström syndrome; new hunger reduction data from the SRC1 and SH2B1 deficiency cohorts in the exploratory Phase 2 Basket Trial; new data on utilization of URO; an analysis of the frequency of melanocortin-4 receptor (MC4R) pathway variants in U.S. patients with severe obesity; and a review of single minded-1 (SIM1) missense variants associated with severe obesity.

- In October, at the Obesity Medicine Association's Overcoming Obesity 2021 Conference (OMA), we presented new HRQOL data from the Phase 3 trials evaluating setmelanotide in POMC or LEPR deficiency obesities that confirmed setmelanotide treatment led to sustained, clinically meaningful HRQOL improvements in a majority of patients; results from in-depth patient interviews conducted in POMC and LEPR patients enrolled in Rhythm's pivotal Phase 3 trials, which highlighted that reduced hunger and improved satiety resulting from setmelanotide treatment substantially and meaningfully changed patients' lives; and two presentations detailing updated results from our URO genetic testing of approximately 8,500 people in the United States with early-onset, severe obesity.

- In September 2021, at the 59th Annual European Society for Paediatric Endocrinology meeting we delivered three oral and four poster presentations, including a new subgroup analysis of data from its Phase 3 clinical trial in BBS, which showed that patients treated with setmelanotide achieved statistically significant weight loss and hunger reduction compared to patients treated with placebo during a 14-week, double-blind treatment period; an interim analyses from our exploratory Phase 2 Basket Trial, which showed that 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 43% (15 of 35) of study participants with obesity due to variants of the SH21B gene, including 16p11.2 chromosomal deletions.

- In September 2021, we announced the promotion of Linda Shapiro Manning, M.D., Ph.D., to Chief Medical Officer. She succeeded Murray Stewart, M.D., who transitioned to the role of Senior Medical Advisor.

On January 5, 2021, we entered into an asset purchase agreement with Alexion Pharmaceuticals, Inc., or Alexion, pursuant to which we agreed to sell our Rare Pediatric Disease Priority Review Voucher, or PRV, to Alexion, or the PRV Transfer. We were awarded the voucher under a FDA program intended to encourage the development of certain rare pediatric disease product applications. We received the PRV when IMCIVREE was approved by the FDA. Pursuant to the transfer agreement, Alexion agreed to pay us $100.0 million in cash upon the closing of the sale. The PRV Transfer closed on February 17, 2021.

On February 9, 2021, we completed an underwritten public offering in which we sold 5,750,000 shares of our common stock at a public offering price of $30.00 per share, which included the exercise in full by the underwriters of their option to purchase up to 750,000 additional shares of common stock. We received aggregate net proceeds from the offering of $161.7 million after deducting underwriting discounts and commissions and offering expenses payable by us.

Our operations to date have been limited primarily to conducting research and development activities for setmelanotide. To date, we have not generated any significant product revenue and have financed our operations primarily through the proceeds received from the sales of common and preferred stock, asset sales, as well as capital contributions from the former parent company, Rhythm Holdings LLC. From August 2015 through August 2017, we raised aggregate net proceeds of $80.8 million through our issuance of series A preferred stock. Since our initial public offering, or IPO, on October 10, 2017 and our underwritten follow-on offerings through February 2021, we have raised aggregate net proceeds of approximately $611.4 million through the issuance of our common stock after deducting underwriting discounts, commissions and offering related transaction costs. As noted above, we also received $100.0 million from an asset sale, specifically in connection with the PRV Transfer. We will not generate significant revenue from product sales until we are able to successfully establish a marketing and commercialization infrastructure for IMCIVREE. IMCIVREE became commercially available to patients 6 years of age and older with obesity due to POMC, PCSK1 or LEPR deficiency in the U.S. in the first quarter of 2021 and following marketing authorizations in the European Union and Great Britain, we are pursuing a country-by-country strategy to establish market access and reimbursement for IMCIVREE in several countries. We expect to continue to fund our operations through the sale of equity, debt financings or other sources. We

intend to build our own marketing and commercial sales infrastructure and we may enter into 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 September 30, 2021 we had an accumulated deficit of $486.1 million. Our net losses were $35.1 million, $33.8 million, $26.7 million and $99.1 million for the three and nine months ended September 30, 2021 and 2020, respectively. We expect to continue to incur significant expenses and increasing operating losses over the foreseeable future. We expect our expenses will increase substantially in connection with our ongoing activities, as we:

- continue to conduct clinical trials for setmelanotide;
- engage contract manufacturing organizations, or CMOs, for the manufacture of clinical and commercial-grade setmelanotide;
- seek regulatory approval for setmelanotide for additional indications;
- expand our clinical, regulatory, commercial and corporate infrastructure and expand operations globally;
- 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 September 30, 2021, our existing cash and cash equivalents and short-term investments were approximately $328.4 million. We expect that our existing cash and cash equivalents and short-term investments will enable us to fund our operating expenses into at least the second half of 2023.

Corporate Background

We are a Delaware corporation organized in February 2013 under the name Rhythm Metabolic, Inc., and as of October 2015, under the name Rhythm Pharmaceuticals, Inc.

Impact of COVID-19

We are closely monitoring how the spread of COVID-19 is affecting our employees, business, preclinical studies and clinical trials. In response to the COVID-19 pandemic, we have limited access to our executive offices with most employees continuing their work outside of our offices and travel has been restricted. Based on current information we do not currently anticipate any disruption in the clinical supply of setmelanotide. Our CMOs have indicated that they have appropriate plans and procedures in place to ensure uninterrupted future supply of clinical and commercial-grade setmelanotide, subject to potential limitations on their operations due to COVID-19. As a result, we do not currently expect that the COVID-19 pandemic will have a material impact on our business, results of operations and financial condition. At this time, however, there is still uncertainty relating to the trajectory of the pandemic and the impact of related responses, and disruptions caused by the COVID-19 pandemic have resulted and may in the future result in difficulties or delays in initiating, enrolling, conducting or completing our planned and ongoing clinical trials and the incurrence of unforeseen costs as a result of disruptions in clinical supply or preclinical study or clinical trial delays. For example, we experienced interruption of key clinical trial activities, such as patient attendance and clinical trial site monitoring, in our Phase 3 clinical trial evaluating setmelanotide for the treatment of insatiable hunger and severe obesity in individuals with BBS or Alström syndrome. The impact of COVID-19 on our future results will largely depend on

future developments, which are highly uncertain and cannot be predicted with confidence, such as the duration of the pandemic, the impact of variants, travel restrictions and social distancing in the United States and other countries, business closures or business disruptions, the ultimate impact on financial markets and the global economy, the effectiveness of vaccines and vaccine distribution efforts and the effectiveness of other actions taken in the United States and other countries to contain and treat the disease. See "Risk Factors—The COVID-19 pandemic has and may continue to adversely impact our business, including our preclinical studies, clinical trials and our commercialization prospects." in Part II, Item 1A of this Quarterly Report on Form 10-Q.

Financial Operations Overview

Revenue

To date, we have not generated significant revenue from product sales. Our lead product candidate, IMCIVREE, was approved by the FDA in November 2020 for chronic weight management in adult and pediatric patients six years of age and older with obesity due to POMC, PCSK1 or LEPR deficiency confirmed by genetic testing. IMCIVREE became commercially available in the U.S. in the first quarter of 2021. We recorded our first sales of IMCIVREE in March 2021. We expect our initial sales of IMCIVREE will be limited by the ultra-rare nature of the disease and limited number of diagnosed patients in the United States.

Cost of sales

All of our inventory of IMCIVREE produced prior to FDA approval is available for commercial or clinical use. Most of the manufacturing costs have been recorded as research and development expenses in prior periods. Accordingly, the costs for IMCIVREE included in our cost of sales for the three months ended September 30, 2021 were insignificant. We expect cost of sales to increase in 2022 as we continue to sell inventory that is produced after we began capitalizing IMCIVREE commercial inventory. The Company is currently evaluating the impact of this previously expensed inventory on the future cost of product sales.

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:

Research and development summary	Three Months Ended September 30, 2021	Three Months Ended September 30, 2020	Nine Months Ended September 30, 2021	Nine Months Ended September 30, 2020
Research and development expense	$ 27,539	$ 22,995	$ 72,554	$ 68,496

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 accelerate our preparation for commercialization and start to market setmelanotide and as we explore new collaborations to develop and commercialize setmelanotide, we anticipate that these expenses will materially increase.

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

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

Selling, general and administrative summary	Three Months Ended September 30, 2021	Three Months Ended September 30, 2020	Nine Months Ended September 30, 2021	Nine Months Ended September 30, 2020
Selling, general and administrative expense	$ 17,507	$ 11,289	$ 47,490	$ 33,006

We anticipate that our selling, general and administrative expenses will increase in the future to support continued and expanding development efforts, commercialization of 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 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.

Except for the application of ASC Topic 606, *Revenue from Contracts with Customers*, that was adopted during the year-ended December 31, 2018 but was not applicable until our first commercial sale, during the nine months ended September 30, 2021, there were no other significant changes to our critical accounting policies as reported in our Annual Report on Form 10-K for the fiscal year ended December 31, 2020.

Results of Operations

Comparison of the three months ended September 30, 2021 and 2020

The following table summarizes our results of operations for the three months ended September 30, 2021 and 2020, together with the changes in those items in dollars and as a percentage:

	Three Months Ended September 30,		Change	
	2021	2020	$	%
	(in thousands)			
Statement of Operations Data:				
Product revenue, net	$ 1,028	$ —	$ 1,028	NM
Costs and expenses:				
Cost of sales	222	—	222	NM
Research and development	27,539	22,995	4,544	20 %
Selling, general, and administrative	17,507	11,289	6,218	55 %
Total costs and expenses	45,268	34,284	10,984	32 %
Loss from operations	(44,240)	(34,284)	(9,956)	29 %
Other income, net	138	466	(328)	(70)%
Loss before taxes	(44,102)	(33,818)	(10,284)	30 %
Benefit from income taxes	(8,995)	—	(8,995)	NM
Net loss	$ (35,107)	$ (33,818)	$ (1,289)	4 %

NM=Not meaningful

Product revenue, net increased to $1.0 million in 2021. There were no product revenues in the comparative prior period. The increase is due to FDA approval of our lead product candidate, IMCIVREE in November 2020. We recorded our first sales of IMCIVREE in March 2021 and the three months ended September 30, 2021 represent our second full quarter of sales subsequent to the launch of IMCIVREE. We expect our initial sales of IMCIVREE will be limited by the

ultra-rare nature of the disease and limited number of diagnosed patients in the United States. To date, all of our product revenue has been generated in the United States.

Cost of sales increased to $0.2 million in 2021. There were no cost of sales in the comparative prior period. All of our inventory of IMCIVREE produced prior to FDA approval is available for commercial or clinical use. Most of the manufacturing costs have been recorded as research and development expenses in prior periods. Accordingly, the costs for IMCIVREE included in our cost of sales for the three months ended September 30, 2021 were insignificant and primarily reflect the amortization of our capitalized sales based milestone payment made to Ipsen upon our first commercial sale as well as a royalty due to Ipsen on our net product sales. We expect cost of sales to increase as we continue to 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 $27.5 million in 2021 from $23.0 million in 2020, an increase of 20%. The increase was primarily due to the following:

- an increase of $4.4 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, QTc study, Phase 2 hypothalamic obesity study, and increased enrollment in our long-term extension study; these increases were partially offset by the conclusion of prior studies, including pivtal Phase 3 studies for POMC and LEPR, as well as GO-ID; and

- an increase of $2.7 million in salaries, benefits and stock-based compensation related to the hiring of additional full-time employees in order to support the growth of our research and development programs;

The above increases were partially offset by:

- a decrease of $1.4 million due to reduced purchases of clinical supply material; and

- a decrease of $0.7 million in costs associated with accessing sequencing data from third-party biobanks to further our genetic research efforts.

Selling, general and administrative expense. Selling, general and administrative expense increased by $6.2 million to $17.5 million in 2021 from $11.3 million in 2020, an increase of 55%. The increase was primarily due to the following:

- an increase of $3.0 million due to increased compensation and benefits related costs associated with additions to our exeutive leadership team, increased headcount to support our expanding business operations as well as to establish commercial operations in the United States and internationally;

- an increase of $1.9 million due to increased professional fees and consulting services to support the build out of our commercial operations in the United States and internationally as well as corporate legal and consulting support for our international expansion; and

- an increase of $0.9 million related to marketing activities for IMCIVREE.

Other income, net. Other income decreased by $0.3 million due to lower interest rates.

Provision for income taxes. We recorded a tax benefit of $9.0 million as a result of our operating expenses incurred during the three months ended September 30, 2021, which offset a portion of the tax provision we recorded as a result of the sale of our PRV. We expect to incurr sufficient operating expenses during the remainder of the current year to offset the income from the sale of our priority review voucher resulting in no current year tax liability.

Net loss. Net loss increased by $1.3 million to $35.1 million in 2021, from $33.8 million in 2020. The increase in net loss was driven by higher operating expenses incurred during the period.

Comparison of the nine months ended September 30, 2021 and 2020

The following table summarizes our results of operations for the nine months ended September 30, 2021 and 2020, together with the changes in those items in dollars and as a percentage:

	Nine Months Ended September 30,		Change	
	2021	2020	$	%
	(in thousands)			
Statement of Operations Data:				
Product Revenue, net	1,337	—	1,337	NM
Operating Expenses:				
Cost of Sales	363	—	363	NM
Research and development	$ 72,554	$ 68,496	$ 4,058	6 %
Selling, general, and administrative	47,490	33,006	14,484	44 %
Total operating expenses	120,407	101,502	18,905	19 %
Loss from operations	(119,070)	(101,502)	(17,568)	17 %
Other income, net	100,313	2,403	97,910	4,074 %
Loss before taxes	(18,757)	(99,099)	80,342	(81)%
Provision for income taxes	7,989	—	7,989	NM
Net loss	$ (26,746)	$ (99,099)	$ 72,353	(73)%

NM=Not meaningful

Product revenue, net increased to $1.3 million in 2021. There were no product revenues in the comparative prior period. The increase is due to FDA approval of our lead product candidate, IMCIVREE in November 2020. We recorded our first sales of IMCIVREE in March 2021 and the three months ended September 30, 2021 represent our second full quarter of sales subsequent to the launch of IMCIVREE. We expect our initial sales of IMCIVREE will be limited by the ultra-rare nature of the disease and limited number of diagnosed patients in the United States. To date, all of our product revenue has been generated in the United States.

Cost of sales increased to $0.4 million in 2021. There were no cost of sales in the comparative prior period. All of our inventory of IMCIVREE produced prior to FDA approval is available for commercial or clinical use. Most of the manufacturing costs have been recorded as research and development expenses in prior periods. Accordingly, the costs for IMCIVREE included in our cost of sales for the three months ended September 30, 2021 were insignificant and cost of sales are primarily comprised of amortization of our capitalized sales based milestone payment due to Ipsen upon our first commercial sale as well as a royalty due to Ipsen on our net product sales. We expect cost of sales to increase as we continue to sell inventory that is produced after we began capitalizing IMCIVREE commercial inventory.

Research and development expense. Research and development expense increased by $4.1 million to $72.6 million in 2021 from $68.5 million in 2020, an increase of 6%. The increase was primarily due to the following:

- an increase of $5.9 million in compensation and benefits due to the hiring of additional full-time employees in order to support the growth of our research and development programs and expansion of regulatory affairs operations; and

- an increase of $2.4 million related to costs associated with new and planned clinical trials, including Phase 2 DAYBREAK and Phase 3 EMANATE trials, Phase 3 pediatrics trial, QTc study, Phase 2 hypothalamic obesity study, and increased enrollment in our long-term extension study. These increases were mostly offset by decreases in our GO-ID study which has been completed;

- an increase of $1.1 million related to costs associated with pursuing the use of setmelanotide in additional indications;

The above increases were partially offset by:

- a decrease of $3.0 million related to a milestone expense associated with the license agreement with Ipsen on filing the NDA with the FDA and filing the MAA with the EMA;
- a decrease of $1.1 million related to lower professional services fees related to regulatory filings;
- a decrease of $0.8 million related to reduced purchases of clinical supply material; and
- a decrease of $0.7 million of costs associated with accessing sequencing data from third-party biobanks to further our genetic research.

Selling, general and administrative expense. Selling, general and administrative expense increased by $14.5 million to $47.5 million in 2021 from $33.0 million in 2020, an increase of 44%. The increase was primarily due to the following:

- an increase of $7.1 million due to increased compensation and benefits related costs associated with additions to our executive leadership team, increased headcount to support our expanding business operations as well as to establish our commercial operations in the United States and internationally;
- an increase of $4.0 million due to increased professional fees and consulting services to support the build out of our commercial operations in the United States and internationally as well as corporate legal and consulting support for our international expansion;
- an increase of $1.6 million associated with the expenses incurred on the sale of our PRV to Alexion;
- an increase of $1.1 million due to increased costs associated with office support and insurance costs for our expanding workforce; and
- an increase of $0.7 million associated with the expenses incurred related to marketing activities for IMCIVREE.

Other income, net. Other income increased by $97.9 million due primarily to the sale of our PRV in February 2021.

Provision for income taxes. We recorded a tax provision of $8.0 million for the period ended September 30, 2021, primarily related to the sale of our PRV, offset by a tax benefit from our ordinary losses. We expect to incurr sufficient operating expenses during the remainder of the current year to offset the income from the sale of our priority review voucher resulting in no current year tax liability.

Net Loss. Net loss decreased by $72.4 million to $26.7 million in 2021, from a loss of $99.1 million in 2020. The decrease in net loss was primarily due to impact of the $100.0 million gain on the sale of our PRV, offset by higher operating expenses and the provision of income taxes recorded recorded as a result sale of the PRV.

Liquidity and Capital Resources

As of September 30, 2021, our cash and cash equivalents and short-term investments were approximately $328.4 million.

Cash flows

The following table provides information regarding our cash flows for the nine months ended September 30, 2021 and 2020:

	Nine Months Ended September 30,	
	2021	2020
	(in thousands)	
Net cash provided by (used in):		
Operating activities	$ (105,531)	$ (92,858)
Investing activities	(69,407)	96,644
Financing activities	166,381	1,589
Net (decrease) increase in cash, cash equivalents and restricted cash	$ (8,557)	5,375

Net cash used in operating activities

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

Net cash used in operating activities was $105.5 million for the nine months ended September 30, 2021 and consisted primarily of a net loss of $102.0 million adjusted for non-cash items, which consisted of non-cash stock-based compensation, the gain on the sale of the PRV, a deferred provision for income taxes, depreciation and amortization and rent expense. The change in operating assets and liabilities reflected a total use of cash of approximately $5.4 million from an increase in accounts payables and accrued expenses associated with our CROs, CMOs and consultants due to the timing of payments, offset by an increase of $8.9 million in prepaid expenses.

Net cash used in operating activities was $92.9 million for the nine months ended September 30, 2020 and consisted primarily of a net loss of $85.6 million adjusted for non-cash items, which consisted of non-cash stock-based compensation, depreciation and amortization and rent expense. The change in operating assets and liabilities reflected a total use of cash of approximately $7.3 million from an increase in prepaid expenses and decreases in accounts payables and accrued expenses associated with our CROs, CMOs and consultants due to the timing of payments.

Net cash (used in) provided by investing activities

Net cash used in investing activities for the nine months ended September 30, 2021 relates to the $164.0 million of net purchases of short-term investments, $0.4 million related to the purchase of property plant and equipment and $5.0 million for the acquisition of an intangible asset, offset by the $100.0 million in proceeds from the sale of the PRV.

Net cash provided by investing activities for the nine months ended September 30, 2020 relates to the net maturities of short-term investments.

Net cash provided by financing activities

Net cash provided by financing activities was $166.4 million for the nine months ended September 30, 2021, which represents the net proceeds of $161.7 million from our common stock offering in February 2021 and $4.7 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 $1.6 million for the nine months ended September 30, 2020, which represents net proceeds from purchases made under the ESPP and proceeds from the exercise of stock options.

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.

We expect that our existing cash and cash equivalents and short-term investments will enable us to fund our operating expenses into at least the second half of 2023. We may need to obtain substantial additional funding in connection with our research and development activities and any continuing operations thereafter. If we are unable to raise capital when needed or on favorable terms, we would be forced to delay, reduce or eliminate our research and development programs or future commercialization efforts.

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

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

Although IMCIVREE has been approved by the FDA and authorized by the EC and Great Britain in certain indications, 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 Quarterly 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 II, Item 1A of this Quarterly Report for a further discussion of the possible impact of the COVID-19 pandemic on our business.

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

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

If we raise funds through additional collaborations, strategic alliances or licensing arrangements with third parties or other means, 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, debt financings or other means, 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

As of September 30, 2021, there were no material changes to our principal contractual obligations and commitments as reported in our Annual Report on Form 10-K for the fiscal year ended December 31, 2020.

Recent Accounting Pronouncements

For a discussion of pending and recently adopted accounting pronouncements, see Note 2 to our unaudited condensed consolidated financial statements included elsewhere in this Quarterly Report on Form 10-Q.

Off-Balance Sheet Arrangements

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

Item 3. Quantitative and Qualitative Disclosures About Market Risk

As of September 30, 2021, there were no material changes to our quantitative and qualitative disclosures about market risks as reported in our Annual Report on Form 10-K for the fiscal year ended December 31, 2020.

Item 4. 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 cost.

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 Quarterly Report on Form 10-Q. Based on such evaluation, our principal executive officer and principal financial officer have concluded that as of September 30, 2021, our disclosure controls and procedures were effective at the reasonable assurance level.

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 most recent fiscal quarter covered by this Quarterly Report on Form 10-Q that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

PART II - OTHER INFORMATION

Item 1. Legal Proceedings

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

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 Quarterly Report on Form 10-Q, including our unaudited condensed consolidated financial statements and the related notes thereto, and "Management's Discussion and Analysis of Financial Condition and Results of Operations."

Risks Related to Our Financial Position and Need for Capital

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

We are a commercial-stage biopharmaceutical company with a limited operating history on which to base your investment decision. Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. We were incorporated in February 2013. Our operations to date have been limited primarily to acquiring rights to intellectual property, business planning, raising capital, developing our technology, identifying potential product candidates, undertaking preclinical studies and conducting research and development activities, including clinical trials, for setmelanotide. To date, we have not generated significant revenue from product sales. We have obtained FDA approval for IMCIVREE for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to proopiomelanocortin, or POMC, proprotein convertase subtilisin/kexin type 1, or PCSK1, or leptin receptor, or LEPR, deficiency confirmed by genetic testing. IMCIVREE has also received authorization by the EC and Great Britain's MHRA for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. We have not obtained any other regulatory approvals for setmelanotide. We first commercialized IMCIVREE in the U.S. in the first quarter of 2021 and therefore do not have a long history operating as a commercial company. We will need to begin transitioning from a company with a research and development focus to a company capable of supporting commercial activities and we may not be successful in such a transition. We have not yet demonstrated our ability to manufacture at commercial scale, or arrange for a third party to do so on our behalf, or conduct sales, marketing and distribution activities necessary for successful product commercialization. Consequently, any predictions made about our future success or viability may not be as accurate as they could be if we had a longer operating history.

Since our inception, we have focused substantially all of our efforts and financial resources on the research and development of setmelanotide, which is approved by the FDA and authorized by the EC and Great Britain's Medicines & Healthcare Products Regulatory Agency, or MHRA, as noted above and currently in regulatory review for Bardet-Biedl syndrome, or BBS, Alström syndrome, and in clinical development for 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 $35.1 million, $33.8 million, $26.7 million, and $99.1 million for the three and nine months ended September 30, 2021 and 2020, respectively. As of September 30, 2021, we had an accumulated deficit of $486.1 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 will incur significant sales, marketing and outsourced manufacturing expenses. We will incur additional costs associated with operating as a public company, including as a result of no longer qualifying as an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. As a result, we expect to continue to incur significant and increasing operating losses for the foreseeable future. Because of the numerous risks and uncertainties associated with developing pharmaceutical products, we are unable to predict the extent of any future losses or when we will become profitable, if at all. Even if we do become profitable, we may not be able to sustain or increase our profitability on a quarterly or annual basis.

Our ability to become profitable depends upon our ability to generate revenue. To date, we have not generated any significant revenue from setmelanotide. Our ability to generate revenue depends on a number of factors, including, but not limited to, our ability to:

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

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

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

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

From August 2015 through August 2017, we raised aggregate net proceeds of $80.8 million through our issuance of series A preferred stock. In connection with our initial public offering, or IPO, in October 2017 and our underwritten follow-on offerings through February 2021, we raised aggregate net proceeds of approximately $611.4 million through the issuance of our common stock after deducting underwriting discounts, commissions and offering related transaction costs. Since inception, we have received a further $100.0 million from asset sales, specifically in connection with the sale of our Rare Pediatric Disease Priority Review Voucher, or PRV, to Alexion Pharmaceuticals, Inc. As of September 30, 2021, our cash and cash equivalents and short-term investments were approximately $328.4 million. We expect our cash and cash equivalents and short-term investments will enable us to fund our operating expenses into at least the second half of 2023. However, our operating plan may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through public or private equity or debt financings, government or other third-party funding, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements, or a combination of these approaches. We will also require additional capital to obtain additional regulatory approvals for, and to continue to commercialize, setmelanotide. Raising funds in the current economic environment, particularly in light of ongoing uncertainty related to the COVID-19 pandemic, may present additional challenges. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or if we have specific strategic considerations.

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

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

Risks Related to the Development of Setmelanotide

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

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

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

We are actively working to advance additional genetic deficiencies related to the MC4R pathway through our clinical development program. Our continued development efforts are focused on obesity related to several single gene-related, or monogenic, MC4R pathway deficiencies: Bardet-Biedl syndrome, or BBS; Alström syndrome; HET obesity due to a genetic variant in one of the two alleles of the POMC, PCSK1 or LEPR gene, or HETs; obesity due to steroid receptor coactivator 1, or SRC1, deficiency; obesity due to SH2B adapter protein 1, or SH2B1, deficiency; hypothalamic obesity; and MC4R deficiency obesity. In August 2021, we announced agreement with the FDA and EMA on the clinical design and primary endpoint of our pivotal Phase 3 EMANATE trial of setmelanotide. The trial is a randomized, double-blind, placebo-controlled study with five independent sub-studies evaluating setmelanotide in patients with: heterozygous POMC/PCSK1 obesity; heterozygous LEPR obesity; certain variants of the SRC1; certain variants of SH2B1 genes; or PCSK1 N221D deletions within the MC4R pathway. Each sub-study will be entirely independent of the others and, if successful, is designed to support separate regulatory submissions to the FDA and EMA in each studied indication. However, the FDA and EMA may not view positive results in one sub-study, even if such results are statistically significant and clinically meaningful, as being sufficient for approval.

Success in a basket trial, or any trial in one indication, may not predict success in another indication. In contrast, in the event of an adverse safety issue, clinical hold, or other adverse finding in one or more indications being tested, such event could adversely affect our trials in the other indications and may delay or prevent completion of such clinical trials.

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

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

timeline and regulatory approval and commercialization prospects for setmelanotide and, correspondingly, our business and financial prospects, would be materially adversely affected.

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

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

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

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

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

The number of patients suffering from each of the MC4R pathway deficiencies we are targeting is small and has not been established with precision. If the actual number of patients is smaller than we estimate, our revenue and ability to achieve profitability may be materially adversely affected.

Due to the rarity of our target indications, there is no comprehensive patient registry or other method of establishing with precision the actual number of patients with MC4R pathway deficiencies. As a result, we have had to rely on other available sources to derive clinical prevalence estimates for our target indications. In addition, we have internal genetic sequencing results from approximately 37,500 patients, as of September 30, 2020, with severe obesity that provide another approach to estimating prevalence. Since the published epidemiology studies for these genetic deficiencies are based on relatively small population samples, and are not amenable to robust statistical analyses, it is possible that these projections may significantly exceed the addressable population, particularly given the need to genotype patients to definitively confirm a diagnosis.

Based on multiple epidemiological methods, we have estimated the potential addressable patient populations with these MC4R pathway deficiencies based on the following sources and assumptions:

- *POMC Deficiency Obesity*. POMC Deficiency Obesity is defined by the presence of biallelic variants in the POMC or PCSK1 genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VOUS). Our addressable patient population estimate for POMC deficiency obesity is approximately 100 to 500 patients in the United States, with a comparable addressable patient population in Europe. Our estimates are based on:
  - approximately 50 patients with POMC deficiency obesity noted in a series of published case reports, each mostly reporting a single or small number of patients. However, we believe our addressable patient population for this deficiency may be approximately 100 to 500 patients in the United States, and a comparable addressable patient population in Europe, as most of the reported cases are from a small number of academic research centers, and because genetic testing for POMC deficiency obesity is often unavailable and currently is rarely performed;
  - our belief, based on discussions with experts in rare diseases, that the number of diagnosed cases could increase several-fold with increased awareness of this deficiency and the availability of new treatments;
  - U.S. Census Bureau figures for adults and children, and Centers for Disease Control and Prevention, or CDC, prevalence numbers for severe adult obese patients (body mass index, or BMI, greater than 40 kg/m^2) and for severe early onset obese children (99th percentile at ages two to 17 years old); and
  - our internal sequencing yield for POMC deficiency obesity patients (including both POMC and PCSK1 gene diseases), defined as patients having biallelic variants in the POMC or PCSK1 genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VOUS), of approximately 0.05%.
- *LEPR Deficiency Obesity*. LEPR Deficiency Obesity is defined by the presence of biallelic variants in the LEPR gene that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VOUS). Our addressable patient population estimate for LEPR deficiency obesity is approximately 500 to 2,000 patients in the United States, with a comparable addressable patient population in Europe. Our estimates are based on:
  - epidemiology studies on LEPR deficiency obesity in small cohorts of patients comprised of children with severe obesity and adults with severe obesity who have a history of early onset obesity;
  - U.S. Census Bureau figures for adults and children and CDC prevalence numbers for severe adult obese patients (BMI, greater than 40 kg/m^2) and for severe early onset obese children (99th percentile at ages two to 17 years old);
  - with wider availability of genetic testing expected for LEPR deficiency obesity and increased awareness of new treatments, our belief that up to 40% of patients with these diseases may eventually be diagnosed; and
  - our internal sequencing yield for LEPR deficiency obesity patients, defined as patients having biallelic variants in the LEPR gene that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VOUS), of approximately 0.09%.

- *Bardet-Biedl Syndrome*. Our addressable patient population estimate for BBS is approximately 1,500 to 2,500 patients in the United States based on:
    - published prevalence estimates of one in 100,000 in North America, which projects to approximately 3,250 people in the United States. We believe the majority of these patients are addressable patients; and
    - our belief that with wider availability of genetic testing expected for BBS and increased awareness of new treatments, the number of patients diagnosed with this disorder will increase.
- *Alström Syndrome*. Our addressable patient population estimate for Alström syndrome is approximately 500 patients in the United States. This estimate is based on:
    - published prevalence estimates of one in 1,000,000 in North America, which projects to approximately 325 people in the United States. We believe the majority of these patients are addressable patients; and
    - our belief that with wider availability of genetic testing expected for Alström syndrome and increased awareness of new treatments, the number of patients diagnosed with this disorder will increase.
- *POMC, PCSK1, or LEPR Heterozygous Deficiency Obesities; SRC1 and SH2B1 Deficiency Obesities*. Our potential setmelanotide-responsive patient population estimate for POMC, PCSK1, or LEPR heterozygous, SRC1 and SH2B1 deficiency obesity patients with at least one variant interpreted as pathogenic, likely pathogenic, or of uncertain significance (VOUS) is 100,000 to 200,000 patients in the United States. Our estimates are based on:
    - U.S. Census Bureau population data and CDC prevalence numbers for early onset obesity (120% the 95th percentile between the ages of 2-5 years);
    - our internal sequencing yield of patients with POMC, PCSK1, or LEPR heterozygous, SRC1 or SH2B1 variants interpreted as pathogenic, likely pathogenic, or of uncertain significance (VOUS) of approximately 10-15%; and
    - a clinical response rate of 40% for patients carrying pathogenic or likely pathogenic variants, and 20% for patients carrying a variant of uncertain significance (VOUS).

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

- *MC4R Deficiency Obesity*. Our addressable patient population estimate for MC4R-rescuable deficiency obesity is approximately 10,000 patients in the United States. This estimate is based on:
    - U.S. Census Bureau population data and CDC prevalence numbers for early onset obesity (120% the 95th percentile between the ages of 2-5 years);
    - a comprehensive ongoing biochemical screening study indicating there may be a defined subset of individuals who carry MC4R variants that may be rescued by an MC4R agonist; and
    - our internal sequencing yield for MC4R deficiency obesity patients of approximately 2.0% prior to application of functional filters.

- *Smith-Magenis Syndrome*. Our addressable patient population estimate for Smith-Magenis syndrome is approximately 2,400 patients in the United States. This estimate is based on:

  - published prevalence estimates of one in 25,000 in the United States, which projects to approximately 13,000 people in the United States;

  - published prevalence estimates that approximately 10% of patients with Smith-Magenis syndrome have RAI1 variants that may affect the MC4R pathway and 90% of patients with Smith-Magenis syndrome have 17p11.2 chromosomal deletions which also may affect the MC4R pathway, of which approximately 67% and 13%, respectively, live with obesity; and

  - U.S. Census Bureau figures for total population of adults and children.

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

Defining the exact genetic variants that result in MC4R pathway 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, and this competition reduces the number and types of patients available to us, as some patients who might have opted to enroll in our trials may instead opt to enroll in a trial being conducted by one of our competitors. Because the number of qualified clinical investigators and clinical trial sites is limited, we expect to conduct some of our clinical trials at the same clinical trial sites that some of our competitors use, which will reduce the number of patients who are available for our clinical trials at such clinical trial sites. In addition, there are limited patient pools from which to draw for clinical studies. In addition to the rarity of genetic diseases of obesity, the eligibility criteria of our clinical studies will further limit the pool of available study participants as we will require that patients have specific characteristics that we can measure or to assure their disease is either severe enough or not too advanced to include them in a study. Patient enrollment for our current or any future clinical trials may be affected by other factors, including:

- size and nature of the patient population;

- severity of the disease under investigation;

- availability and efficacy of approved drugs for the disease under investigation;

- patient eligibility criteria for the trial in question as defined in the protocol;

- perceived risks and benefits of the product candidate under study;

- clinicians' and patients' perceptions as to the potential advantages of the product candidate being studied in relation to other available therapies, including any new products that may be approved or future product candidates being investigated for the indications we are investigating;

- clinicians' willingness to screen their patients for genetic markers to indicate which patients may be eligible for enrollment in our clinical trials;

- delays in or temporary suspension of the enrollment of patients in our planned clinical trial due to the COVID-19 pandemic;

- ability to obtain and maintain patient consents;

- patient referral practices of physicians;

- the ability to monitor patients adequately during and after treatment;

- proximity and availability of clinical trial sites for prospective patients; and

- the risk that patients enrolled in clinical trials will drop out of the trials before completion, including as a result of contracting COVID-19 or other health conditions or being forced to quarantine, or, because they may be late-stage cancer patients, will not survive the full terms of the clinical trials.

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

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

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

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

- inability to generate sufficient preclinical or other in vivo or *in vitro* data to support the initiation of clinical studies;

- delays in the completion of preclinical laboratory tests, animal studies and formulation studies in accordance with FDA's good laboratory practice requirements and other applicable regulations;

- the FDA or other equivalent competent authorities in foreign jurisdictions may deny permission to proceed with our ongoing or planned trials or any other clinical trials we may initiate, or may place a clinical trial on hold or be suspended;

- delays in filing or receiving authorization to proceed under an additional investigational new drug application, or IND, if required;
- delays in reaching a consensus with the FDA and other regulatory agencies on study design and obtaining regulatory authorization to commence clinical trials;
- delays in reaching or failing to reach agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- difficulties in obtaining Institutional Review Board, or IRB, and/or ethics committee approval to conduct a clinical trial at a prospective site or sites;
- since many already diagnosed patients are at academic sites, delays in conducting clinical trials at academic sites due to the particular challenges and delays typically associated with those sites, as well as the lack of alternatives to these sites which have already-diagnosed patients;
- inadequate quantity or quality of setmelanotide or other materials necessary to conduct clinical trials, including delays in the manufacturing of sufficient supply of finished drug product;
- challenges in identifying, recruiting and training suitable clinical investigators;
- challenges in recruiting and enrolling suitable patients to participate in clinical trials;
- severe or unexpected drug-related side effects experienced by patients in a clinical trial, including side effects previously identified in our completed clinical trials;
- difficulty collaborating with patient groups and investigators;
- failure by our CROs, other third parties or us to perform in accordance with the FDA's or any other regulatory authority's good clinical practice requirements, or GCPs, or applicable regulatory guidelines in other countries;
- occurrence of adverse events associated with setmelanotide that are viewed to outweigh its potential benefits, or occurrence of adverse events in trial of the same or similar class of agents conducted by other companies;
- changes to the clinical trial protocols;
- clinical sites deviating from trial protocol or dropping out of a trial;
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols;
- changes in the standard of care on which a clinical development plan was based, which may require new or additional trials;
- selection of clinical endpoints that require prolonged periods of observation or analyses of resulting data;
- the cost of clinical trials of our product candidates being greater than we anticipate;
- clinical trials of our product candidates producing negative or inconclusive results, which may result in our deciding, or regulators requiring us, to conduct additional clinical trials or abandon development of such product candidates; and

- development of antibodies to the drug or adjuvants may result in loss of efficacy or safety events.

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

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

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

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

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

- delays in receiving approval from local regulatory authorities to initiate or conduct our planned clinical trials;
- further delays or difficulties in enrolling patients in our clinical trials;

- delays or difficulties in clinical site initiation, including difficulties in recruiting clinical site investigators and clinical site staff;

- delays in clinical sites receiving the supplies and materials needed to conduct our clinical trials, including interruption in global shipping that may affect the transport of clinical trial materials;

- changes in local regulations as part of a response to the COVID-19 pandemic which may require us to change the ways in which our clinical trials are conducted, which may result in unexpected costs, or to discontinue such clinical trials altogether;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

congestive heart failure and potentially other conditions, may confound the understanding of the safety profile of setmelanotide.

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

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

- regulatory authorities may request that we withdraw the product from the market or may limit or vary their approval of the product through labeling or other means;
- regulatory authorities may require the addition of labeling statements, such as a “boxed” warning or a contraindication;
- the FDA, the European Commission and other equivalent competent authorities in foreign jurisdictions may require the addition of a Risk Evaluation and Mitigation Strategy, or REMS, or other specific obligations as a condition for marketing authorization due to the need to limit treatment to rare patient populations, or to address safety concerns;
- we may be required to change the way the product is distributed or administered or change the labeling of the product;
- we may be required to conduct additional studies and clinical trials or comply with other post-market requirements to assess possible serious risks;
- we may be required to conduct long term safety follow-up evaluations, including setting up disease and drug based registries;
- we may decide to remove the product from the marketplace;
- we could be sued and held liable for injury caused to individuals exposed to or taking the product; and
- our reputation may suffer.

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

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

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

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

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

In the EU, orphan drug designation is granted by the European Commission based on a scientific opinion by the EMA's Committee for Orphan Medicinal Products in relation to medicinal products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than five in 10,000 persons in the EU and in relation to which no satisfactory method of diagnosis, prevention, or treatment has been authorized (or the product would be a significant benefit to those affected). Additionally, designation is granted for products intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the medicinal product in the EU would be sufficient to justify the necessary investment in developing the medicinal product.

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

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

We have been granted orphan drug designation for setmelanotide in treating POMC deficiency obesity, LEPR deficiency obesity, BBS and Alström syndrome in both the United States and the EU. We have been granted orphan designation for setmelanotide in treating Prader-Willi syndrome in the EU. There can be no assurance that the FDA or the European Commission will grant such designation for setmelanotide for other uses. In addition, orphan drug designation

neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process.

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

Although we have obtained PRIME designation in the EU and Breakthrough Therapy designation for setmelanotide for the treatment of obesity associated with certain genetic defects upstream of the MC4R in the leptin-melanocortin pathway, which includes POMC deficiency obesity, LEPR deficiency obesity, Bardet-Biedl syndrome and Alström syndrome in the United States, the FDA may rescind the Breakthrough Therapy Designation and we may be unable to obtain Breakthrough Therapy designation for other uses. In addition, Breakthrough Therapy designation by the FDA 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 program was launched by the EMA in 2016. PRIME is intended to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimize development plans and speed up evaluation so these medicines can reach patients earlier. In late June 2018, setmelanotide was designated as PRIME by the CHMP. Acknowledging that setmelanotide targets an unmet medical need, the EMA offers enhanced support in the development of the medicinal product through enhanced interaction and early dialogue to optimize our development plans and speed up regulatory evaluation in the EU. As part of this designation, the EMA has provided guidance to us concerning the development of setmelanotide. The PRIME designation does not, however, guarantee that the regulatory review process in the EU will be shorter or less demanding. Neither does the PRIME designation guarantee that the European Commission will grant addtional 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. 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-

formulation that may be well-received by patients.

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

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

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

Our approach to treating patients with MC4R pathway deficiencies requires the identification of patients with unique genetic subtypes, for example, POMC genetic deficiency. The FDA or other equivalent competent authorities in foreign jurisdictions could require the clearance, approval or CE marking of an in vitro companion diagnostic device to ensure appropriate selection of patients as a condition of approving setmelanotide in additional indications. The requirement that we obtain clearance, approval or CE mark of an in vitro companion diagnostic device will require substantial financial resources, and could delay or prevent the receipt of additional regulatory approvals for setmelanotide, or adversely affect those we have already obtained.

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

If the FDA or a comparable regulatory authority requires clearance or approval of a companion diagnostic for setmelanotide, any delay or failure by us or our current and future collaborators to develop or obtain regulatory clearance or approval of, or to CE mark, such tests, if necessary, could delay or prevent us from obtaining additional approvals for setmelanotide, or adversely affect the approvals we have already obtained. For example, in November 2020, the FDA approved IMCIVREE for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to POMC, PCSK1, or LEPR deficiencies confirmed by genetic testing demonstrating variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance. Although the FDA did not require that we obtain approval of a companion diagnostic prior to approving the New Drug Application, or NDA, for IMCIVREE, in connection with the NDA approval we agreed as a post-marketing commitment to conduct adequate analytical and clinical validation testing to develop and establish an *in vitro* companion diagnostic device to accurately and reliably detect patients with variants in the *POMC*, *PCSK1*, and *LEPR* genes that may benefit from setmelanotide therapy. In September 2020, our collaboration partner, Prevention Genetics, submitted a de novo request seeking FDA authorization to market such an *in vitro* companion diagnostic device for IMCIVREE as a Class II medical device. In

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

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

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

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

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

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

Risks Related to the Commercialization of IMCIVREE (setmelanotide)

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

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

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

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

In some foreign countries, particularly in Canada, 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 setmelanotide with other available therapies. If reimbursement for setmelanotide is unavailable in any country in which we seek reimbursement, if it is limited in scope or amount, if it is conditioned upon our completion of additional clinical trials or if pricing is set at unsatisfactory levels, our operating results could be materially adversely affected.

In the EU, in particular, each EU member state can restrict the range of medicinal products for which its national health insurance system provides reimbursement and can control the prices of medicinal products for human use marketed in its territory. As a result, following receipt of marketing authorization in an EU member state, through any application route, an applicant is required to engage in pricing discussions and negotiations with the competent pricing authority in

the individual EU member states. Some EU member states operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed upon. Other EU member states approve a specific price for the medicinal product or may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. The downward pressure on healthcare costs in general, particularly prescription drugs, has become more intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, we may face competition for setmelanotide from lower priced products in foreign countries that have placed price controls on pharmaceutical products.

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

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

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

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

We may never receive regulatory approval to market setmelanotide outside of the United States, the European Union and Great Britain.

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

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

The commercial success of IMCIVREE will also depend upon the awareness and acceptance of setmelanotide within the medical community, including physicians, patients and third-party payors. If IMCIVREE does not achieve an adequate level of acceptance by patients, physicians and third-party payors, we may not generate sufficient revenue to become or remain profitable. Before granting reimbursement approval, third-party payors may require us to demonstrate that, in addition to treating obesity caused by certain genetic deficiencies affecting the MC4R pathway, IMCIVREE also provides incremental health benefits to patients. Our efforts to educate the medical community and third-party payors about the benefits of IMCIVREE may require significant resources and may never be successful. All of these challenges may impact our ability to ever successfully market and sell IMCIVREE.

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

- the ability of IMCIVREE to provide chronic weight management in patients with obesity caused by certain genetic deficiencies affecting the MC4R pathway and, if required by any competent authority in connection with the approval for these indications, to provide patients with incremental health benefits, as compared with other available treatments, therapies, devices or surgeries;
- the complexities of genetic testing, including obtaining genetic results that support patient treatment with IMCIVREE;
- the relative convenience and ease of SC injections as the necessary method of administration of IMCIVREE, including as compared with other treatments for obese patients;
- the prevalence and severity of any adverse side effects associated with IMCIVREE;
- limitations or warnings contained in the labeling approved for IMCIVREE by the FDA or the specific obligations imposed as a condition for marketing authorization imposed by other equivalent competent authorities in foreign jurisdictions, particularly by the European Commission;
- availability of alternative treatments, including a number of obesity therapies already approved or expected to be commercially launched in the near future;

- our ability to increase awareness of these diseases among our target populations through marketing and other cross-functional efforts;
- the size of the target patient population, and the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the ability of IMCIVREE to treat the maximum range of pediatric patients, and any limitations on its indications for use;
- the strength of marketing and distribution support and timing of market introduction of competitive products;
- publicity concerning IMCIVREE or competing products and treatments;
- pricing and cost effectiveness;
- the effectiveness of our sales and marketing strategies;
- our ability to increase awareness of IMCIVREE through marketing efforts;
- our ability to obtain sufficient third-party coverage or reimbursement;
- the willingness of patients to pay out-of-pocket in the absence of third-party coverage; and
- the likelihood that competent authorities in foreign jurisdictions may require development of a REMS as a condition of approval or post-approval, may not agree with our proposed REMS or may impose additional requirements that limit the promotion, advertising, distribution or sales of setmelanotide.

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

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

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

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

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

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

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

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

We do not currently have, nor do we plan to acquire, the infrastructure or capability to manufacture our clinical and commercial drug supply internally for setmelanotide, or any future product candidates, for use in the conduct of our preclinical studies and clinical trials, and we lack the internal resources and the capability to manufacture any product candidate on a clinical or commercial scale. The facilities used by our contract manufacturing organizations, or CMOs, to manufacture the active pharmaceutical ingredient, or API, and final drug product must pass inspection by the FDA and other equivalent competent authorities in foreign jurisdictions pursuant to inspections that have been and will be conducted following submission of our NDAs or relevant foreign regulatory submission to the other equivalent competent authorities

in foreign jurisdictions. Our failure or the failure of our CMOs to pass preapproval inspection of the manufacturing facilities of setmelanotide could delay the regulatory approval process. In addition, our clinical trials must be conducted with products produced under cGMP regulations. Our failure or the failure of our CROs or CMOs to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process and could also subject us to enforcement action, including civil and criminal penalties. When we import any drugs or drug substances, we would be subject to FDA, United States Department of Agriculture, and U.S. Bureau of Customs and Border Patrol import regulation requirements. Such enforcement for our failure or our CROs or CMOs' failure to comply with these regulations could result in import delays, detention of products, and, depending on criteria such as the history of violative activities, the FDA could place a foreign firm or certain drug substances or products on Import Alert and require that all such drug substances or products be subject to detention without physical examination which could significantly impact the global supply chain for setmelanotide. With the exception of those on the FDA's drug shortage list or properly imported by individuals, the FDCA prohibits the importation of prescription drug products for commercial use if they were manufactured in a foreign country, unless they have been approved or are otherwise authorized to be marketed in the United States and are labeled accordingly.

We currently contract with third parties for the manufacture of setmelanotide and intend to continue to do so in the future. We have entered into process development and manufacturing service agreements with our CMOs, Corden Pharma 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, or PPL, 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 cGMPs 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 cGMPs, and, therefore, the company's management practices and oversight, including routine auditing, are critical. If our CMOs cannot successfully manufacture material that conform to our specifications and the strict regulatory requirements of the FDA or other equivalent competent authorities in foreign jurisdictions, they may be subject to administrative and judicial enforcement for non-compliance and the drug products would be deemed misbranded or adulterated and prohibited from distribution into interstate commerce. Furthermore, all of our CMOs are engaged with other companies to supply and/or manufacture materials or products for such companies, which exposes our manufacturers to regulatory risks for the production of such materials and products. As a result, failure to satisfy the regulatory requirements for the production of those other company materials and products may affect the regulatory clearance of our CMOs' facilities generally. In addition, satisfying the regulatory requirements for production of setmelanotide with multiple suppliers, while assuring more robust drug availability in the future, adds additional complexity and risk to regulatory approval. If the FDA or another equivalent competent foreign regulatory agency does not approve these facilities for the manufacture of setmelanotide or if it withdraws its approval in the future, we may need to find alternative manufacturing facilities, which would adversely impact our ability to develop, obtain regulatory approval for or market setmelanotide.

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

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

We do not have long-term supply agreements in place with 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 may have to approve these changes. We plan to continue to rely upon CMOs and, potentially, collaboration partners to manufacture commercial quantities of setmelanotide. Our current scale of manufacturing appears adequate to support all of our current needs for clinical trial and initial commercial supplies for setmelanotide. Going forward, we may need to identify additional CMOs or partners to produce setmelanotide on a larger scale.

Risks Related to Our Intellectual Property Rights

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

Our commercial success will depend in part on our success in obtaining and maintaining issued patents and other intellectual property rights in the United States and elsewhere and protecting our proprietary technology. If we do not adequately protect our intellectual property and proprietary technology, competitors may be able to use our technologies and erode or negate any competitive advantage we may have, which could harm our business and ability to achieve profitability.

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

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

decision in an interference proceeding can result in a third party receiving the patent right sought by us, which in turn could affect our ability to develop, market or otherwise commercialize setmelanotide.

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

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

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

- any of our patents, or any of our pending patent applications, if issued, will include claims having a scope sufficient to protect setmelanotide;
- any of our pending patent applications will issue as patents;
- we will be able to successfully commercialize IMCIVREE before our relevant patents expire;
- we were the first to make the inventions covered by each of our patents and pending patent applications;
- we were the first to file patent applications for these inventions;
- others will not develop similar or alternative technologies that do not infringe our patents;
- any of our patents will be found to ultimately be valid and enforceable;
- any patents issued to us will provide a basis for an exclusive market for our commercially viable products, will provide us with any competitive advantages or will not be challenged by third parties;
- we will develop additional proprietary technologies or product candidates that are separately patentable; or
- our commercial activities or products will not infringe upon the patents of others.

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

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

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

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

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

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

Our success will depend in part on our ability to operate without infringing the intellectual property and proprietary rights of third parties. We cannot assure you that our business, products and methods do not or will not infringe the patents or other intellectual property rights of third parties. For example, numerous third-party U.S. and non-U.S. patents and pending applications exist that cover melanocortin receptor analogs and methods of using these analogs.

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

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

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

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

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

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

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

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

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

If we or one of our licensing partners threatened or initiated legal proceedings against a third party to enforce a patent covering setmelanotide, the defendant could claim that the patent covering setmelanotide is invalid and/or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge include alleged failures to meet any one of several statutory requirements, including novelty, non-obviousness and enablement. Grounds for unenforceability assertions include allegations that someone connected with prosecution of the patent withheld material information from the U.S. PTO, or made a misleading statement, during patent prosecution. Third parties may also raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, *inter partes* review, post grant review and equivalent proceedings in foreign jurisdictions, for example, opposition proceedings. Such proceedings could result in revocation or amendment of our patents in such a way that they no longer cover setmelanotide or competitive products. The outcome following legal assertions of invalidity and/or unenforceability is unpredictable. With respect to validity, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on setmelanotide. Such a loss of patent protection would have a material adverse impact on our business.

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

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

that in the United States. These products may compete with our product and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

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

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

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

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

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

While we have registered trademarks for the commercial trade name IMCIVREE (setmelanotide) in the United States, 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, 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.

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

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

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

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

In the EU, the grant of orphan designation for setmelanotide means that this medicinal product would be entitled, upon grant of marketing authorization by the European Commission, to ten years of exclusivity in all EU member states. Marketing authorization may, however, be granted to a similar medicinal product with the same orphan indication during the ten year period if we are unable to supply sufficient quantities of setmelanotide. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if the similar product is deemed safer, more effective or otherwise clinically superior to setmelanotide. The period of market exclusivity may, in addition, be reduced to six years if it can be demonstrated on the basis of available evidence that setmelanotide is sufficiently profitable not to justify maintenance of market exclusivity.

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

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

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

Congress, the federal courts and the U.S. PTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents or future patents.

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

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

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

Even if we complete the necessary clinical trials, the regulatory and marketing approval process is expensive, time consuming and uncertain and may prevent us from obtaining additional approvals for the commercialization of setmelanotide beyond FDA approval for obesity due to POMC, PCSK1or LEPR deficiencies in the United States and the grant of marketing authorization by the European Commission and the MHRA for the treatment of obesity and the control of hunger associated with confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above in the European Union and Great Britain, respectively. We depend entirely on the success of setmelanotide, and we cannot be certain that we will be able to obtain additional regulatory approvals for, or successfully commercialize, setmelanotide. If we are not able to obtain, or if there are delays in obtaining, required additional regulatory approvals, we will not be able to commercialize setmelanotide in additional indications in the United States or in foreign jurisdictions, and our ability to generate revenue will be materially impaired.

We currently have only one product candidate, setmelanotide, in clinical development, and our business depends entirely on its successful clinical development, regulatory approval and commercialization. Setmelanotide, which is currently approved by FDA for chronic weight management in patients with obesity due to POMC, PCSK1 or LEPR deficiencies and the European Commission and MHRA granted marketing authorization to setmelanotide for the treatment of obesity and the control of hunger associated with confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above, will require substantial additional clinical development, testing and regulatory approval before we are permitted to commence commercialization in indications beyond those currently approved for IMCIVREE in the United States, the European Union 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 non-clinical testing and clinical trials that the product candidate is safe and effective for use in each target indication. This process can take many years and approval, if any, may be conditional on post-marketing studies and surveillance, and will require the expenditure of substantial resources beyond our existing cash resources. Of the large number of drugs in development in the United States and in other countries, only a small percentage will successfully complete the FDA regulatory approval process or the equivalent process in foreign jurisdictions and will be commercialized. In addition, we have not discussed all of our proposed development programs with the FDA of the competent authorities of foreign jurisdictions. Accordingly, even if we are able to obtain the requisite financing to continue to fund our development and clinical trials, we cannot assure you that setmelanotide will be successfully developed or commercialized.

In addition, obtaining FDA approval of an NDA for additional indications and the approval of an MAA from the European Commission for additional indications is a complex, lengthy, expensive and uncertain process, and the FDA,

EMA or equivalent competent authorities in foreign jurisdictions may delay, limit or deny approval of setmelanotide for many reasons, including, among others:

- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may disagree with our interpretation of data from clinical trials, or may change the requirements for approval even after it has reviewed and commented on the design for our clinical trials;
- we may not be able to demonstrate to the satisfaction of the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions that setmelanotide is safe and effective in treating obesity caused by certain genetic deficiencies affecting the MC4R pathway;
- the results of our clinical trials may not be interpretable or meet the level of statistical or clinical significance required by the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions for marketing approval. For example, the potential unblinding of setmelanotide studies due to easily identifiable AEs may raise the concern that potential bias has affected the clinical trial results;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may disagree with the number, size, conduct or implementation of our clinical trials;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may require that we conduct additional clinical trials or pre-clinical studies;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may not consider that our diagnostic strategy supports approval;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may decide that additional assays or data to understand any risks for anti-drug antibodies may need to be available for approval;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may decide that the toxicology program, including any parts of carcinogenicity studies that are filed, do not meet the requirements for approval;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions or the applicable foreign regulatory agency may identify deficiencies in our chemistry, manufacturing or controls of setmelanotide, or in the commercial production of setmelanotide to support product approval;
- the CROs that we retain to conduct our clinical trials may take actions outside of our control that materially adversely impact our clinical trials;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may find the data from preclinical studies and clinical trials insufficient to demonstrate that clinical and other benefits of setmelanotide outweigh its safety risks;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may disagree with our interpretation of data from our preclinical studies and clinical trials;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may not approve the formulation, labeling or specifications of setmelanotide;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may not accept data generated at our clinical trial sites;

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

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

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

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

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

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

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

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

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

Separately, in response to COVID-19, on March 10, 2020 the FDA announced its intention to postpone most foreign inspections of manufacturing facilities and products through April 2020, and subsequently, on March 18, 2020, the FDA temporarily postponed routine surveillance inspections of domestic manufacturing facilities. Subsequently, on July 10, 2020 the FDA announced its intention to resume certain on-site inspections of domestic manufacturing facilities subject to a risk-based prioritization system. The FDA intends to use this risk-based assessment system to identify the categories of regulatory activity that can occur within a given geographic area, ranging from mission critical inspections to resumption of all regulatory activities. In addition, on April 15, 2021, the FDA issued a guidance document in which the FDA outlined plans to conduct voluntary remote interactive evaluations of certain drug manufacturing facilities and clinical research sites. According to the guidance, the FDA intends to request such remote interactive evaluations in situations where an in-person inspection would not be prioritized, deemed mission-critical or is otherwise limited by travel restrictions, but where the FDA determines that a remote evaluation would still be appropriate. Regulatory authorities outside the United States may adopt similar restrictions or other policy measures in response to the COVID-19 pandemic.

If a prolonged government shutdown occurs, or if global health concerns continue to prevent the FDA or other regulatory authorities from conducting their regular inspections, reviews, or other regulatory activities, it could significantly impact the ability of the FDA or other regulatory authorities to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

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

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

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

Regulatory authorities may impose significant restrictions on setmelanotide's indicated uses or marketing or impose ongoing requirements for potentially costly post approval studies. We and setmelanotide will also be subject to ongoing requirements by the FDA, the European Commission, the EMA, and the competent authorities in the EU member states, governing labeling, packaging, storage, advertising, promotion, marketing, distribution, importation, exportation, post-approval changes, manufacturing, recordkeeping, and submission of safety and other post market information. Advertising and promotional materials must comply with the FDCA and implementing regulations, and are subject to FDA oversight and post-marketing reporting obligations, in addition to other potentially applicable federal and state laws. The FDA and the other competent foreign authorities have significant post market authority, including, for example, the authority to require labeling changes based on new safety information and to require post market studies or clinical trials to evaluate serious safety risks related to the use of a drug. The FDA also has the authority to require, as part of an NDA or post approval, the submission of a REMS, which may include Elements to Assure Safe Use. Any REMS required by the FDA may lead to increased costs to assure compliance with new post approval regulatory requirements and potential requirements or restrictions on the sale of approved products, all of which could lead to lower sales volume and revenue.

The holder of an approved NDA also must submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process, or adding new manufacturers.

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

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

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

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

In addition, a sponsor’s responsibilities and obligations under the FDCA and FDA regulations, and those of equivalent foreign regulatory agencies, may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. For example, the results of the 2020 U.S. Presidential Election may impact our business and industry. Namely, the Trump administration took several executive actions, including the issuance of a number of Executive Orders, that could impose significant burdens on, or otherwise materially delay, the FDA’s ability to engage in routine oversight activities such as implementing statutes through rulemaking, issuance of guidance, and review and approval of marketing applications. It is difficult to predict whether or how these orders will be implemented, or whether they will be rescinded and replaced under the Biden administration. The policies and priorities of the new administration are unknown and could materially impact the regulations governing our product candidates. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may be subject to enforcement action and we may not achieve or sustain profitability.

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

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

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

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

In March 2010, 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" from the 340B ceiling price requirements for these covered entities;

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

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

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

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

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. For example, beginning April 1, 2013, Medicare payments to providers were reduced by 2% under the sequestration required by the Budget Control Act of 2011, which will remain in effect through 2030, with the exception of a temporary suspension from May 1, 2020 through December 31, 2021 due to the COVID-19 pandemic. On January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Moreover, the federal government and the individual states in the United States have become increasingly active in developing proposals, passing legislation and implementing regulations designed to control drug pricing, including price or patient reimbursement constraints, discounts, formulary flexibility, marketing cost disclosure and transparency measures. These initiatives may result in additional reductions in Medicare and other healthcare funding and, if we obtain regulatory approvals, may otherwise affect the prices we may obtain for setmelanotide or the frequency with which setmelanotide is prescribed or used if approved.

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

regulatory requirements on our activities or result in reduced reimbursement for our products, any of which could adversely affect our business, results of operations and financial condition.

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

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

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

We intend to participate in and have certain price reporting obligations to the Medicaid Drug Rebate Program The Medicaid Drug Rebate Program requires participating manufacturers to pay a rebate to each state Medicaid program for covered outpatient drugs that are dispensed to Medicaid beneficiaries and paid for by a state Medicaid. Those rebates are based on pricing data that must be reported on a monthly and quarterly basis to the CMS, the federal agency that administers the Medicaid Drug Rebate Program. These data include the average manufacturer price and, in the case of innovator products, the best price for each drug which, in general, represents the lowest price available from the manufacturer to any entity in the U.S. in any pricing structure, calculated to include all sales and associated rebates, discounts and other price concessions. Our failure to comply with these price reporting and rebate payment obligations could negatively impact our financial results.

The ACA made significant changes to the Medicaid Drug Rebate Program, as described under the risk factor "*Current and future healthcare reform legislation or regulation may increase the difficulty and cost for us and any future collaborators to obtain marketing approval of and commercialize setmelanotide and may adversely affect the prices we, or they, may obtain and may have a negative impact on our business and results of operations*," above. 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' Medicaid Drug Rebate Program rebate liability, effective January 1, 2024. Under current law enacted as part of the ACA, drug manufacturers' Medicaid Drug Rebate Program rebate liability is capped at 100% of the average manufacturer price for a covered outpatient drug. Congress could enact additional legislation that further increases Medicaid drug rebates or other costs and charges associated with participating in the Medicaid Drug Rebate Program. Additional legislation or the issuance of regulations relating to the Medicaid Drug Rebate Program could have a material adverse effect on our results of operations.

Federal law requires that any company that participates in the Medicaid Drug Rebate Program also participate in the 340B program in order for federal funds to be available for the manufacturer's drugs under Medicaid and Medicare Part B. The 340B program, which is administered by the Health Resources and Services Administration, or HRSA, requires

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

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

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

CMS and the Department of Health & Human Services Office of Inspector General have pursued manufacturers that were alleged to have failed to report these data to the government in a timely manner. Governmental agencies may also make changes in program interpretations, requirements or conditions of participation, some of which may have implications for amounts previously estimated or paid. We cannot assure you that any submissions we are required to make under the Medicaid Drug Rebate Program and consequently the 340B program will not be found to be incomplete or incorrect.

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

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

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

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

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

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

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

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

governing the promotion of medicinal products in the EU could be penalized by administrative measures, fines and imprisonment. These laws may further limit or restrict the advertising and promotion of our products to the general public and may also impose limitations on our promotional activities with health care professionals.

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

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

- The United States federal healthcare Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, or receiving remuneration, (anything of value), directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, lease order or arranging for or recommending the purchase, lease or order of any good or service for which payment may be made, in whole or in part, by federal healthcare programs such as Medicare and Medicaid. This statute has been interpreted to apply to arrangements between pharmaceutical companies on one hand and prescribers, purchasers, formulary managers, and patients on the other. Liability under the Anti-Kickback Statute may be established without proving actual knowledge of the statute or specific intent to violate it. 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) and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Beginning in 2022, applicable manufacturers also will be required to report information regarding payments and transfers of value provided to physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, anesthesiology assistants and certified nurse-midwives. Manufacturers must submit reports on or before the 90th day of each calendar year disclosing reportable payments made in the previous calendar year.

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

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

Ensuring that our business arrangements and interactions with healthcare professionals, third-party payors, patients and others comply with applicable healthcare laws and regulations will require substantial resources. Various state

and federal regulatory and enforcement agencies continue actively to investigate violations of health care laws and regulations, and the United States Congress continues to strengthen the arsenal of enforcement tools.

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 Quarterly Report.

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

We are subject to U.S. data protection laws and regulations, for example, laws and regulations that address privacy and data security, at both the federal and state levels. The legislative and regulatory landscape for data protection continues to evolve, and in recent years there has been an increasing focus on privacy and data security issues. Numerous federal and state laws, including state data breach notification laws, state health information privacy laws, state genetic privacy laws, and federal and state consumer protection laws, including, for example, Section 5 of the Federal Trade Commission Act of 1914, as amended, and the California Consumer Privacy Act, or the CCPA as well as the California Privacy Rights Act, or the CPRA govern the collection, use, and disclosure and protection of certain health-related and other personal information. Failure to comply with data protection laws and regulations could result in government enforcement actions and create liability for us, which could include civil and/or criminal penalties, private litigation and/or adverse publicity that could negatively affect our operating results and business. In addition, we may obtain health information from third parties, such as research institutions with which we collaborate, that are subject to privacy and security requirements under HIPAA. Although we are not directly subject to HIPAA, other than potentially with respect

to providing certain employee benefits, we could be subject to criminal penalties if we knowingly obtain or disclose individually identifiable health information maintained by a HIPAA covered entity in a manner that is not authorized or permitted by HIPAA. In addition, state laws govern the privacy and security of health, research and genetic information in specified circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. Some of our research activities involve minors, which may be subject to additional laws and can require specialized consent processes, privacy protections, and compliance procedures.

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

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

With respect to the transfer of personal data out of the EU and the United Kingdom, the GDPR and the United Kingdom GDPR provide that the transfer of personal data to countries that are not considered by the European Commission or the United Kingdom government, as applicable, to provide an adequate level of data protection, including the United States, is permitted only on the basis of complying with specific legal steps, a number of which are subject to legal challenges. Most recently, on July 16, 2020, the Court of Justice of the European Union, or the CJEU, invalidated the EU-US Privacy Shield Framework, or the Privacy Shield, under which personal data could be transferred from the EEA to US entities who had self-certified under the Privacy Shield scheme and imposed further restrictions on the use of the standard contractual clauses, or SCCs. These restrictions include a requirement for companies to carry out a transfer impact assessment which, among other things, assesses the laws governing access to personal data in the recipient country and considers whether supplementary measures that provide privacy protections additional to those provided under SCCs will need to be implemented to ensure an essentially equivalent level of data protection to that afforded in the EEA. The European Commission issued revised SCCs on June 4, 2021 to account for the decision of the CJEU and recommendations made by the European Data Protection Board. The revised SCCs must be used for relevant new data transfers from September 27, 2021; existing standard contractual clauses arrangements must be migrated to the revised clauses by December 27, 2022. There is some uncertainty around whether the revised clauses can be used for all types of data transfers, particularly whether they can be relied on for data transfers to non-EEA entities subject to the GDPR. As supervisory authorities issue further guidance on personal data export mechanisms, including circumstances where the standard contractual clauses cannot be used, and/or start taking enforcement action, we could suffer additional costs, complaints and/or regulatory investigations or fines, and/or if we are otherwise unable to transfer personal data between and among countries and regions in which we operate, it could affect the manner in which we provide our services, the geographical location or segregation of our relevant systems and operations, and could adversely affect our financial

results. The European Commission has adopted an adequacy decision in favor of the UK, enabling data transfers from EU member states to the UK without additional safeguards. However, the UK adequacy decision will automatically expire in June 2025 unless the European Commission re-assesses and renews/extends that decision.

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

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

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

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

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

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

If we expand our operations outside of the United States, we must dedicate additional resources to comply with numerous laws and regulations in each jurisdiction in which we plan to operate. The Foreign Corrupt Practices Act of 1977, or the FCPA, prohibits any U.S. individual or business from paying, offering, authorizing payment or offering anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of such third party in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with certain accounting

provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the company, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations.

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

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

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

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

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

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

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

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

Risks Related to Employee Matters and Managing Growth

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

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

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

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

The physical expansion of our operations may lead to significant costs and may divert financial resources from other projects, such as the development of setmelanotide. Many of our suppliers and collaborative and clinical trial relationships are located outside the United States, and we may in the future seek to hire employees located outside of the United States. Accordingly, our business may become subject to economic, political, regulatory and other risks associated with international operations, such as compliance with tax, employment, immigration and labor laws for employees living

or traveling abroad, workforce uncertainty in countries where labor unrest is more common than in the United States, as well as difficulties associated with staffing and managing international operations, including differing labor relations. Any of these factors could materially affect our business, financial condition and results of operations. Our future financial performance and our ability to commercialize setmelanotide, if approved, and compete effectively will depend, in part, on our ability to effectively manage the future development and expansion of our company.

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

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

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

Risks Related to Our Common Stock

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

Our executive officers and directors and their respective affiliates, in the aggregate, hold shares representing approximately 11.9% of our outstanding voting stock as of September 30, 2021. As a result, if these stockholders were to choose to act together, they would be able to significantly influence all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these stockholders could significantly influence elections of directors, any amendments of our organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may feel are in your best interest as one of our stockholders.

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

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

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

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

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

- discussion of us or our stock price by the press and by online investor communities; and
- other risks and uncertainties described in these risk factors.

Our quarterly operating results may fluctuate significantly.

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

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

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

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

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

If a corporation undergoes an "ownership change," very generally defined as a greater than 50% change by value in its equity ownership by certain shareholders or groups of shareholders over a rolling three-year period, Sections 382 and 383 of the Code limit the corporation's ability to use carryovers of its pre-change NOLs, credits and certain other tax attributes to reduce its tax liability for periods after the ownership change. Our issuance of common stock pursuant to prior public offerings may have resulted in a limitation under Code Sections 382 and 383, either separately or in combination with certain prior or subsequent shifts in the ownership of our common stock. Future changes in our stock ownership, some of which are outside of our control, could also result in an ownership change under Sections 382 and 383 of the Code. In addition, for taxable years beginning after December 31, 2020, utilization of federal NOLs generated in tax years beginning after December 31, 2017 are limited to a maximum of 80% of the taxable income for such year, after taking into account utilization of NOLs generated in years beginning before January 1, 2018 and determined without regard to such NOL deduction. Further regulatory changes could also limited our ability to utilize our NOLs. As a result, our ability

to use carryovers of NOLs and credits to reduce our future U.S. federal income tax liability may be subject to limitations. This could result in increased U.S. federal income tax liability for us if we generate taxable income in a future period. Limitations on the use of NOLs and other tax attributes could also increase our state tax liability. Any such limitation could have a material adverse effect on our results of operations in future years. We have not completed a study to assess whether an ownership change for purposes of Section 382 or 383 has occurred, or whether there have been multiple ownership changes since our inception, due to the significant costs and complexities associated with such study.

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

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

Sales of our common stock in the public market, or the perception that these sales could occur, could cause the market price of our common stock to decline significantly. As of September 30, 2021, we had 50,268,312 shares of common stock outstanding.

The holders of an aggregate of approximately 5.9 million shares of our common stock, or approximately 11.8% of our total outstanding common stock as of September 30, 2021, are entitled to rights with respect to the registration of their shares under the Securities Act, subject to specified conditions, until such shares can otherwise be sold without restriction under Rule 144 or until the rights terminate pursuant to the terms of the investors' rights agreement between us and such holders. We have also registered and intend to continue to register all shares of common stock that we may issue under our equity compensation plans. Once we register these shares under the Securities Act, the shares become freely tradable without restriction under the Securities Act, except for shares purchased by affiliates. Any sales of securities by these stockholders could have a material adverse effect on the trading price of our common stock.

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

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

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

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

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

We have never declared or paid any cash dividends on our common stock and do not currently intend to do so in the foreseeable future. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends in the foreseeable future. Therefore, the success of an investment in shares of our common stock will depend upon any future appreciation in their value. There is no guarantee that shares of our common stock will appreciate in value or even maintain the price at which you purchased them.

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

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

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

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

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

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

Our certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for: (i) any derivative action or proceeding brought on our behalf; (ii) any action asserting a claim of breach of fiduciary duty; (iii) any action asserting a claim against us arising under the DGCL, our certificate of incorporation or our bylaws; and (iv) any action asserting a claim against us that is governed by the internal affairs doctrine. In addition, our bylaws provide that the federal district courts of the United States are the exclusive forum for any complaint raising a cause of action arising under the Securities Act. Any person or entity purchasing or otherwise acquiring any interest in any

of our securities shall be deemed to have notice of and consented to the provisions of our certificate of incorporation and bylaws described above. These exclusive-forum provisions may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage lawsuits against us and our directors, officers and other employees. If a court were to find these provisions of our certificate of incorporation or bylaws to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving the dispute in other jurisdictions, which could seriously harm our business.

General Risk Factors

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

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

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

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

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

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

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

We may seek additional capital through a combination of private and public equity offerings, debt financings, collaborations and strategic and licensing arrangements. To the extent that we raise additional capital through the sale of common stock or securities convertible or exchangeable into common stock, a stockholder's ownership interest in our company will be diluted. In addition, the terms of any such securities may include liquidation or other preferences that materially adversely affect the rights of our stockholders. Debt financing, if available, would increase our fixed payment obligations and may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through collaboration, strategic partnerships and licensing arrangements with third parties, we may have to relinquish valuable rights to setmelanotide, our intellectual property or future revenue streams, or grant licenses on terms that are not favorable to us.

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

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

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

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

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

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

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

Pursuant to Section 404, we are required to furnish a report by our management on our internal control over financial reporting. To continue to achieve compliance with Section 404, we continue to be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude that our internal control over financial reporting is effective as required by Section 404.

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

Item 2. Unregistered Sales of Equity Securities and Use of Proceeds

Unregistered Sales of Equity Securities

None.

Use of Proceeds

Not applicable.

Purchases of Equity Securities by the Issuer and Affiliated Purchasers

None.

Item 3. Defaults Upon Senior Securities

Not applicable.

Item 4. Mine Safety Disclosure

Not applicable.

Item 5. Other Information

None.

Item 6. Exhibits

Exhibit Number	Exhibit Description	Incorporated by Reference		
		Form	Date	Number
3.1	Amended and Restated Certificate of Incorporation.	10-Q	05/04/2020	3.1
3.2	Amended and Restated Bylaws.	8-K	12/11/2020	3.1
4.1*	Amendment No. 1 to Amended and Restated Investors' Rights Agreement, dated January 25, 2021.			
10.1	Offer Letter, dated July 9, 2021, by and between the Registrant and Pamela Cramer.	10-Q	08/03/2021	10.1
10.2*	Offer Letter, dated September 1, 2021, by and between the Registrant and Linda Shapiro Manning, M.D.			
31.1*	Certification of the Principal Executive Officer, as required by Section 302 of the Sarbanes-Oxley Act of 2002 (18 U.S.C. 1350).			
31.2*	Certification of the Principal Financial Officer, as required by Section 302 of the Sarbanes-Oxley Act of 2002 (18 U.S.C. 1350).			
32.1**	Certification of the Principal Executive Officer, as required by Section 906 of the Sarbanes-Oxley Act of 2002 (18 U.S.C. 1350).			
32.2**	Certification of the Principal 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).			

* Filed herewith.

** Furnished herewith.

SIGNATURES

Pursuant to the requirements of the Securities Exchange 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.

Dated: November 2, 2021

By: /s/ David P. Meeker, M.D.
Name: David P. Meeker, M.D.
Title: President and Chief Executive Officer
(Principal Executive Officer)

Dated: November 2, 2021

By: /s/ Hunter C. Smith
Name: Hunter C. Smith
Title: Chief Financial Officer and Treasurer
(Principal Financial Officer)

RHYTHM PHARMACEUTICALS, INC.

AMENDMENT NO. 1 TO
AMENDED AND RESTATED INVESTORS' RIGHTS AGREEMENT

This Amendment No. 1 to Amended and Restated Investors' Rights Agreement (this "***Amendment***") is entered into as of January 25, 2021, by and among Rhythm Pharmaceuticals, Inc., a Delaware corporation (the "***Company***"), and the undersigned Investors (the "***Amending Investors***") party to that certain Amended and Restated Investors' Rights Agreement, dated as of August 21, 2017 (the "***Investors' Rights Agreement***"), by and among the Company and the Investors named therein. Capitalized terms used and not defined herein shall have the respective meanings assigned to such terms in the Investors' Rights Agreement.

WHEREAS, the Company previously entered into the Investors' Rights Agreement;

WHEREAS, Section 6.6 of the Investors' Rights Agreement provides that the Investors' Rights Agreement generally may be amended with the written consent of (i) the Company and (ii) the holders of a majority of the Registrable Securities then outstanding and held by the Holders (collectively, the "***Required Parties***"); and

WHEREAS, the Amending Investors constitute the Required Parties, and the Company and the Required Parties desire to amend the Investors' Rights Agreement as set forth below.

NOW, THEREFORE, in consideration of the foregoing, the Company and the undersigned Amending Investors agree as follows:

1. AMENDMENTS

(a) The definition of "Registrable Securities" in Section 1 of the Investors' Rights Agreement is hereby amended and restated in its entirety to read as follows:

> ""**Registrable Securities**" means (i) the Common Stock issuable or issued upon conversion of any series of Preferred Stock; (ii) any Common Stock held by the Investors as of immediately prior to the closing of the IPO; (iii) any Common Stock issued or issuable (directly or indirectly) upon conversion and/or exercise of any other securities of the Company held by the Investors as of immediately prior to the closing of the IPO; and (iv) any Common Stock issued as (or issuable upon the conversion or exercise of any warrant, right, or other security that is issued as) a dividend or other distribution with respect to, or in exchange for or in replacement of, the securities referenced in clauses (i), (ii) and (iii) above; provided, however, Registrable Securities shall exclude, in all cases, (x) any shares sold or otherwise disposed of by a Person in a transaction in which the applicable rights under this Agreement are not assigned pursuant to Subsection 6.1 or (y) any shares for which registration rights have terminated pursuant to Section 2.13 of this Agreement."

(b) Section 2.13 of the Investors' Rights Agreement is hereby amended and restated in its entirety to read as follows:

> "2.13 Termination of Registration Rights. The right of any Holder to request registration or inclusion of Registrable Securities in any registration pursuant to Subsections 2.1 or 2.2

of this Agreement or to receive any notices hereunder or to vote, consent to, waive or otherwise exercise any rights with respect to any amendment, consent, waiver or other right hereunder shall terminate, and any shares held by a Holder shall cease to be Registrable Securities, upon the earliest to occur of:

(a) the closing of a Deemed Liquidation Event, as such term is defined in the Restated Certificate, as amended and in effect from time to time;

(b) such time as either (i) Rule 144 or another similar exemption under the Securities Act is available for the sale of all of such Holder's shares without limitation during a three-month period without registration and without the requirement for the Company to be in compliance with the current public information required under Rule 144(c)(1) or (ii) such Holder no longer holds any Registrable Securities;

(c) the fifth (5th) anniversary of the closing of the IPO; and

(d) such time as the Holder is not an Affiliate of the Company."

2. MISCELLANEOUS.

Each of the undersigned Amending Investors represents and warrants to the Company, severally and not jointly, that the number of shares of Common Stock that it holds on the date hereof is set forth on the applicable signature page hereto.

Except as specifically amended herein, the Investors' Rights Agreement is hereby ratified and confirmed and shall remain in full force and effect. Each reference in the Investors' Rights Agreement to "this Agreement," "hereunder," "hereof," "herein" or words of like import shall mean and be a reference to the Investors' Rights Agreement, as amended by this Amendment.

This Amendment and any controversy arising out of or relating to this Amendment shall be governed by and construed in accordance with the internal laws of the State of Delaware, without regard to conflict of law principles that would result in the application of any law other than the law of the State of Delaware.

This Amendment may be executed in several counterparts (including by facsimile or other electronic means), each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

[Signature Page Follows]

IN WITNESS WHEREOF, each undersigned Investor has executed this Amendment as of the date first written above.

NEW ENTERPRISE ASSOCIATES 13, L.P.

By: NEA Partners 13, L.P., its General Partner

By: NEA 13 GP, LTD, its General Partner

By: /s/ Louis Citron
Name: Louis S. Citron
Title: Chief Legal Officer

Registrable Securities Held at IPO: 4,362,306
Registrable Securities Sold: 0
Total Registrable Securities Held on Date Hereof: 4,909,956

NEA VENTURES 2009, LIMITED PARTNERSHIP

By: /s/ Louis Citron
Name: Louis S. Citron
Title: Vice President

Registrable Securities Held at IPO: 0
Registrable Securities Sold: 0
Total Registrable Securities Held on Date Hereof: 2,350

IN WITNESS WHEREOF, each undersigned Investor has executed this Amendment as of the date first written above.

MPM BIOVENTURES V, L.P.

By: MPM BIOVENTURES V GP LLC, its General Partner

By: MPM BIOVENTURES V LLC, its Managing Member

By: /s/ Nicholas McGrath
Name: Nicholas McGrath
Title: Authorized Signatory

Registrable Securities Held at IPO: 2,959,906
Registrable Securities Sold: 1,122,046
Total Registrable Securities Held on Date Hereof: 1,837,860

MPM ASSET MANAGEMENT INVESTORS BV5 LLC

By: MPM BIOVENTURES V LLC, its Manager

By: /s/ Nicholas McGrath
Name: Nicholas McGrath
Title: Authorized Signatory

Registrable Securities Held at IPO: 114,987
Registrable Securities Sold: 43,589
Total Registrable Securities Held on Date Hereof: 71,398

IN WITNESS WHEREOF, each undersigned Investor has executed this Amendment as of the date first written above.

/s/ David Meeker
David Meeker

Registrable Securities Held at IPO: 76,335
Registrable Securities Sold: 0
Total Registrable Securities Held on Date Hereof: 76,335

IN WITNESS WHEREOF, each undersigned Investor has executed this Amendment as of the date first written above.

/s/ Keith Gottesdiener
Keith Gottesdiener

Registrable Securities Held at IPO: 585,539
Registrable Securities Sold: 79,500
Total Registrable Securities Held on Date Hereof: 506,039

Acknowledged and Agreed:

RHYTHM PHARMACEUTICALS, INC.

By: /s/ David Meeker
Name: David Meeker
Title: President and CEO

[Rhythm Pharmaceuticals. – Signature Page to Amendment No. 1 to Investors' Rights Agreement]

September 1, 2021

RE: Chief Medical Officer Appointment

Dear Linda,

Congratulations on your promotion to Chief Medical Officer with Rhythm Pharmaceuticals, Inc. (referred to in this letter as "Rhythm" or the "Company") effective September 10, 2021, reporting to David Meeker, President & Chief Executive Officer. Below you will find important information about your position, rewards and benefits. All other terms and conditions, other than those expressly outlined in this letter, remain the same from your original offer letter dated June 16, 2021.

Employment. 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. In this role, your salary will be $450,000 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, during each 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 will be increased to 40% of your annualized base salary. Any annual bonus for fiscal 2021 may be prorated based on the length of your service as Senior Vice President, Clinical and Chief Medical Officer, respectively, during 2021.

Signing Bonus. You acknowledge that the Company paid to you a one-time cash signing bonus of $90,000, less applicable withholdings, in connection with your commencement of employment (the "Signing Bonus"). In the event you resign or are terminated for Cause (as defined below) within twenty-four (24) months following your employment commencement date, you will be required to repay the gross amount of the Signing Bonus within ninety (90) days of your termination date. In addition, as set forth in your original offer letter, the Company will pay you a one-time cash signing bonus of $15,000, less applicable withholdings, should you relocate to Boston, Massachusetts within the first year of your employment. Such payment will be made within [thirty (30)] days of your relocation, subject to your continued employment through such payment date.

Equity Grant. In addition to your new hire grant in your original offer letter, the Company will grant to you 15,000 stock options and 2,500 restricted stock units, subject to the approval of the Board of Directors of the Company. The stock options and restricted stock units will be subject to the terms of the Company's 2017 Equity Incentive Plan and an award agreement to be entered into between you and the Company.

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. Per your original offer letter, you will be eligible for annual paid vacation of four (4) weeks. Your accrual and use of vacation time will be pursuant and subject to any vacation or time off policy the Company may establish or modify from time to time. The Company's vacation policy and your vacation entitlement are subject to change at any time in the Company's sole discretion.

Severance. If the Company terminates your employment without Cause or you resign your employment with the Company for Good Reason (in either event, a "Qualifying Termination"), then, subject to your execution of a general release of claims 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 "Severance Amount").

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 timely 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 Severance Amount, provide you with severance pay in an amount equal to your then-current base salary rate for a period of nine (9) 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 (the "Change of Control Severance Amount").

In addition, in the event of your Qualifying Termination, if following your Separation from Service, you are eligible for and timely elect continued medical insurance coverage pursuant to COBRA, then, subject to your timely 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 reimburse you for or pay on your behalf 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.

Any Severance Amount or Change of Control 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 sixty (60) days after the date of your Separation from Service and with the first installment to include any amounts that would otherwise have been payable prior to such first payroll date. To be eligible for any Severance Amount, Change in Control Severance Amount or COBRA reimbursement hereunder, you must execute and deliver the Release to the Company and allow it to become effective within thirty (30) days following your Separation from Service.

If a 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 shall immediately vest and, if applicable, become exercisable with respect to one hundred percent (100%) of the shares 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. 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 Internal Revenue Code of 1986, as amended (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. In no event may you, directly or indirectly, designate the calendar year of any payment to be made to you under this letter, to the extent such payment is subject to Section 409A of the Code. The Company makes no representations or warranty and shall have no liability to you or any other person if any provisions of this letter are determined to constitute deferred compensation subject to Section 409A of the Code but do not satisfy an exemption from, or the conditions of, Section 409A of the Code. 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 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.

Parachute Payments. Notwithstanding any other provisions of this letter, any Company plan or any other agreement, in the event that any payment or benefit by the Company or otherwise to or for the benefit of you, whether paid or payable or distributed or distributable pursuant to the terms of this letter or otherwise (all such payments and benefits, including the severance payments and benefits hereunder, being hereinafter referred to as the "Total Payments"), would be subject (in whole or in part) to the excise tax imposed by Section 4999 of the Code (the "Excise Tax"), then the Total Payments shall be reduced (in the order provided below) to the minimum extent necessary to avoid the imposition of the Excise Tax on the Total Payments, but only if (i) the net amount of such Total Payments, as so reduced (and after subtracting the net amount of federal, state and local income and employment taxes on such reduced Total Payments and after taking into account the phase out of itemized deductions and personal exemptions attributable to such reduced Total Payments), is greater than or equal to (ii) the net amount of such Total Payments without such reduction (but after subtracting the net amount of federal, state and local income and employment taxes on such Total Payments and the amount of the Excise Tax to which you would be subject in respect of such unreduced Total Payments and after taking into account the phase out of itemized deductions and personal exemptions attributable to such unreduced Total Payments).

The Total Payments shall be reduced in the following order: (i) reduction on a pro-rata basis of any cash severance payments that are exempt from Section 409A of the Code, (ii) reduction on a pro-rata basis of any non-cash severance payments or benefits that are exempt from Section 409A of the Code, (iii) reduction on a pro-rata basis of any other payments or benefits that are exempt from Section 409A of the Code and (iv) reduction of any payments or benefits otherwise payable to you on a pro-rata basis or such other manner that complies with Section 409A of the Code; provided, in case of clauses (ii), (iii) and (iv), that reduction of any payments attributable to the acceleration of vesting of Company equity awards shall be first applied to Company equity awards that would otherwise vest last in time.

All determinations regarding the application of this Parachute Payments section shall be made by an accounting firm or consulting group with experience in performing calculations regarding the applicability of Section 280G of the Code and the Excise Tax selected by the Company (the "Independent Advisors"). For purposes of determinations, no portion of the Total Payments shall be taken into account which, in the opinion of the

Independent Advisors, (i) does not constitute a "parachute payment" within the meaning of Section 280G(b)(2) of the Code (including by reason of Section 280G(b)(4)(A) of the Code) or (ii) constitutes reasonable compensation for services actually rendered, within the meaning of Section 280G(b)(4)(B) of the Code, in excess of the "base amount" (as defined in Section 280G(b)(3) of the Code) allocable to such reasonable compensation. The costs of obtaining such determination and all related fees and expenses (including related fees and expenses incurred in any later audit) shall be borne by the Company.

In the event it is later determined that a greater reduction in the Total Payments should have been made to implement the objective and intent of this Parachute Payments section, you agree to promptly return the excess amount to the Company.

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.

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.

Cause. "Cause" shall mean the occurrence of any of the following events: (i) your commission of any crime involving the Company, or any crime involving fraud, breach of trust, physical or emotional harm to any person, moral turpitude or dishonesty; (ii) any unauthorized use or disclosure by you 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 by you 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) your repeated and willful failure to perform the duties, functions and responsibilities of your 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 proportionally 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 Financial Officer 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.

Invention, Non-Disclosure, Non-Competition and Non-Solicitation Obligations. The Employee Confidentiality, Assignment of Inventions, Non-Competition and Non-Solicitation Agreement in the form attached hereto as Exhibit A (the "NDA") that you executed and delivered for the benefit of the Company in connection with your original offer letter, dated June 17, 2021, remains in full effect.

Representation. You hereby represent and warrant to the Company that the execution, delivery and performance of this letter by you do not and shall not conflict with, breach, violate or cause a default under any contract, agreement, instrument, order, judgment or decree to which you are a party or by which you are bound.

Amendment. The provisions of this letter may be amended or waived only with the prior written consent of the Company and you, and no course of conduct or course of dealing or failure or delay by you or the Company in enforcing or exercising any of the provisions of this letter shall affect the validity, binding effect or enforceability of the letter or be deemed to be an implied waiver of any similar or dissimilar requirement, provision or condition of this letter at the same or any prior or subsequent time.

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, with the exception that all other terms and conditions, other than those expressly outlined in this letter, remain the same from your original offer letter.

Sincerely,

David Meeker
President & Chief Executive Officer

The foregoing correctly sets forth the terms of my at-will employment with Rhythm. I am not relying on any representations other than those set forth above.

Linda Shapiro	Date

Exhibit 31.1

CERTIFICATION

I, David P. Meeker, certify that:

1. I have reviewed this quarterly report on Form 10-Q 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: November 2, 2021

/s/ David P. Meeker, M.D.
Name: David P. Meeker, M.D.
Title: President and Chief Executive Officer
(*Principal Executive Officer*)

Exhibit 31.2

CERTIFICATION

I, Hunter C. Smith, certify that:

1. I have reviewed this quarterly report on Form 10-Q 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: November 2, 2021

/s/ Hunter C. Smith
Name: Hunter C. Smith
Title: Chief Financial Officer and Treasurer
(*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 the best of my knowledge, the Quarterly Report on Form 10-Q of Rhythm Pharmaceuticals, Inc. for the fiscal quarter ended September 30, 2021 (the "Report") fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, and the information contained in the Report 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: President and Chief Executive Officer
(*Principal Executive Officer*)

November 2, 2021

Exhibit 32.2

CERTIFICATION OF CHIEF FINANCIAL OFFICER
PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

I, Hunter C. Smith, certify pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to the best of my knowledge, the Quarterly Report on Form 10-Q of Rhythm Pharmaceuticals, Inc. for the fiscal quarter ended September 30, 2021 (the "Report") fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934 and the information contained in the Report 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 and Treasurer
(*Principal Financial Officer*)

November 2, 2021