

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 March 31, 2020
OR

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

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

RHYTHM PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction of
incorporation or organization)

46-2159271
(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:

Table with 3 columns: Title of each class, Trading Symbol(s), Name of each exchange on which registered. Row 1: 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 [X] 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 [X] 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 [X]
Non-accelerated filer [] Smaller reporting company [X]
Emerging growth company [X]

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. [X]

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes [] No [X].

The number of shares outstanding of the registrant's Common Stock as of April 24, 2020 was 44,091,798.

RHYTHM PHARMACEUTICALS, INC.

FORM 10-Q

INDEX

	<u>Page No.</u>
<u>PART I FINANCIAL INFORMATION</u>	
<u>Item 1. Condensed Consolidated Financial Statements (Unaudited)</u>	3
<u>Condensed Consolidated Balance Sheets</u>	3
<u>Condensed Consolidated Statements of Operations and Comprehensive Loss</u>	4
<u>Condensed Consolidated Statements of Stockholders' Equity</u>	5
<u>Condensed Consolidated Statements of Cash Flows</u>	6
<u>Notes to Unaudited Condensed Consolidated Financial Statements</u>	7
<u>Item 2. Management's Discussion and Analysis of Financial Condition and Results of Operations</u>	15
<u>Item 3. Quantitative and Qualitative Disclosures About Market Risk</u>	23
<u>Item 4. Controls and Procedures</u>	23
<u>PART II OTHER INFORMATION</u>	23
<u>Item 1. Legal Proceedings</u>	23
<u>Item 1A. Risk Factors</u>	24
<u>Item 2. Unregistered Sales of Equity Securities and Use of Proceeds</u>	86
<u>Item 3. Defaults Upon Senior Securities</u>	86
<u>Item 4. Mine Safety Disclosure</u>	86
<u>Item 5. Other Information</u>	86
<u>Item 6. Exhibits</u>	87
<u>SIGNATURES</u>	88

PART I – FINANCIAL INFORMATION**Item 1. Financial Statements**

Rhythm Pharmaceuticals, Inc.
Condensed Consolidated Balance Sheets
(in thousands, except share and per share data)

(Unaudited)

	<u>March 31,</u> <u>2020</u>	<u>December 31,</u> <u>2019</u>
Assets		
Current assets:		
Cash and cash equivalents	\$ 55,776	\$ 62,294
Short-term investments	201,648	230,165
Prepaid expenses and other current assets	10,436	9,945
Total current assets	267,860	302,404
Property and equipment, net	3,504	3,671
Right-of-use asset	1,989	2,045
Restricted cash	403	403
Total assets	<u>\$ 273,756</u>	<u>\$ 308,523</u>
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	\$ 5,932	\$ 10,415
Accrued expenses and other current liabilities	11,277	13,530
Lease liability	487	472
Total current liabilities	17,696	24,417
Long-term liabilities:		
Lease liability	2,959	3,086
Total liabilities	20,655	27,503
Commitments and contingencies		
Stockholders' equity:		
Preferred Stock, \$0.001 par value: 10,000,000 shares authorized; no shares issued and outstanding at March 31, 2020 and December 31, 2019, respectively	—	—
Common stock, \$0.001 par value: 120,000,000 shares authorized; 44,088,390 and 43,996,753 shares issued and outstanding March 31, 2020 and December 31, 2019, respectively	44	44
Additional paid-in capital	612,552	606,307
Accumulated deficit	(359,495)	(325,331)
Total stockholders' equity	253,101	281,020
Total liabilities and stockholders' equity	<u>\$ 273,756</u>	<u>\$ 308,523</u>

The accompanying notes are an integral part of these 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 March 31,	
	2020	2019
Operating expenses:		
Research and development	\$ 22,504	\$ 22,761
Selling, general, and administrative	12,796	7,759
Total operating expenses	<u>35,300</u>	<u>30,520</u>
Loss from operations	(35,300)	(30,520)
Other income (expense):		
Interest income, net	1,136	1,546
Total other income, net	<u>1,136</u>	<u>1,546</u>
Net loss	<u>\$ (34,164)</u>	<u>\$ (28,974)</u>
Net loss per share, basic and diluted	<u>\$ (0.78)</u>	<u>\$ (0.84)</u>
Weighted-average common shares outstanding, basic and diluted	<u>44,049,843</u>	<u>34,417,189</u>
Other comprehensive loss:		
Net loss	\$ (34,164)	\$ (28,974)
Unrealized gain on marketable securities	63	—
Comprehensive loss	<u>\$ (34,101)</u>	<u>\$ (28,974)</u>

The accompanying notes are an integral part of these financial statements

Rhythm Pharmaceuticals, Inc.

Condensed Consolidated Statements of Stockholders' Equity

(in thousands, except share data)

(Unaudited)

	Common Stock		Additional Paid-In Capital	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount			
Balance at December 31, 2019	43,996,753	\$ 44	\$ 606,307	\$ (325,331)	\$ 281,020
Stock compensation expense	—	—	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
Change in unrealized gain (loss) on marketable securities	—	—	63	—	63
Net loss	—	—	—	(34,164)	(34,164)
Balance at March 31, 2020	<u>44,088,390</u>	<u>\$ 44</u>	<u>\$ 612,552</u>	<u>\$ (359,495)</u>	<u>\$ 253,101</u>
Balance at December 31, 2018	34,410,725	\$ 34	\$ 430,824	\$ (184,602)	\$ 246,256
Stock compensation expense	—	—	2,644	—	2,644
Issuance of common stock in connection with ESPP	12,105	—	295	—	295
Issuance of common stock in connection with exercise of stock options	7,811	—	54	—	54
Change in unrealized gain (loss) on marketable securities	—	—	214	—	214
Net loss	—	—	—	(28,974)	(28,974)
Balance at March 31, 2019	<u>34,430,641</u>	<u>\$ 34</u>	<u>\$ 434,031</u>	<u>\$ (213,576)</u>	<u>\$ 220,489</u>

The accompanying notes are an integral part of these financial statements

Rhythm Pharmaceuticals, Inc.
Condensed Consolidated Statements of Cash Flows
(in thousands)
(Unaudited)

	<u>Three months ended March 31,</u>	
	<u>2020</u>	<u>2019</u>
Operating activities		
Net loss	\$ (34,164)	\$ (28,974)
Adjustments to reconcile net loss to cash used in operating activities:		
Stock-based compensation expense	5,475	2,644
Depreciation and amortization	167	245
Non-cash rent expense	(56)	102
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	(847)	(3,321)
Accounts payable, accrued expenses and other current liabilities	(6,673)	(2,074)
Net cash used in operating activities	<u>(36,098)</u>	<u>(31,378)</u>
Investing activities		
Purchases of short-term investments	(15,370)	(55,819)
Maturities of short-term investments	44,243	80,171
Purchases of property and equipment	—	(811)
Net cash used in investing activities	<u>28,873</u>	<u>23,541</u>
Financing activities		
Proceeds from the exercise of stock options	383	21
Proceeds from issuance of common stock from ESPP	324	295
Net cash provided by financing activities	<u>707</u>	<u>316</u>
Net increase in cash, cash equivalents and restricted cash	(6,518)	(7,521)
Cash, cash equivalents and restricted cash at beginning of year	62,697	49,943
Cash, cash equivalents and restricted cash at end of year	<u>\$ 56,179</u>	<u>\$ 42,422</u>

The accompanying notes are an integral part of these 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 late-stage biopharmaceutical company focused on the development and commercialization of therapeutics for the treatment of rare genetic disorders which are characterized by early-onset, severe obesity and an insatiable hunger or hyperphagia. The Company’s lead product candidate is setmelanotide, a potent melanocortin-4 receptor, or MC4R, agonist for the treatment of rare genetic disorders of obesity. We believe setmelanotide, 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.

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

The Company has also acquired exclusive, worldwide rights from Takeda Pharmaceutical Company Limited, or Takeda, to develop and commercialize T-3525770, now RM-853. RM-853 is a potent, orally available ghrelin o-acyltransferase inhibitor currently in preclinical development for Prader-Willi Syndrome, or PWS. PWS is a rare genetic disorder that results in hyperphagia and early-onset, life-threatening obesity, for which there are no approved therapeutic options.

The Company is subject to risks and uncertainties common to late-stage companies in the biotechnology industry, including but not limited to, risks associated with 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. Product candidates currently under development will require significant additional research and development efforts, including preclinical and clinical testing and regulatory approval, prior to commercialization. These efforts require significant amounts of additional capital, adequate personnel and infrastructure and extensive compliance-reporting capabilities. Even if the Company’s product development efforts are successful, it is uncertain when, if ever, the Company will realize revenue from product sales.

Corporate Reorganization

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. Prior to its organization and a corporate reorganization, the Company was part of Rhythm Pharmaceuticals, Inc., a Delaware corporation which was organized in November 2008 and which commenced active operations in 2010.

Liquidity

The Company has incurred operating losses and negative cash flows from operations since inception. As of March 31, 2020, the Company had an accumulated deficit of \$359,495. The Company has primarily funded these losses through the proceeds from the sales of common and preferred stock as well as capital contributions received from the

former parent company, Rhythm Holdings LLC. To date, the Company has no product revenue and management expects operating losses to continue for the foreseeable future. The Company has devoted substantially all of its resources to its drug development efforts, comprising of research and development, manufacturing, conducting clinical trials for its product candidates, protecting its intellectual property, pre-commercialization activities and general and administrative functions relating to these operations. The future success of the Company is dependent on its ability to develop its product candidates and ultimately upon its ability to attain profitable operations. At March 31, 2020, the Company had \$257,424 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, and funded research and development programs, to maintain the Company's operations and meet the Company's obligations. There is no guarantee that additional equity or other financings will be available to the Company on acceptable terms, or at all. If the Company fails to obtain additional funding when needed, the Company would be forced to scale back, terminate its operations or seek to merge with or be acquired by another company. Management believes that the Company's existing cash resources will be sufficient to fund the Company's operations through at least the end of 2021.

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 March 31, 2020, the statements of operations and comprehensive loss for the three months ended March 31, 2020 and 2019, the statement of stockholders equity and the statement of cash flows for the three months ended March 31, 2020 and 2019 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, 2019 and include all adjustments, which are all normal recurring adjustments necessary for the fair presentation of the interim financial statements. The results for the three months ended March 31, 2020 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 March 31, 2020, 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, 2019.

Use of Estimates

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

Changes in estimates are recorded in the period in which they become known. Actual results could differ materially from those estimates.

Principles of Consolidation

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

Off-Balance Sheet Risk and Concentrations of Credit Risk

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

Segment Information

Operating segments are defined as components of an entity about which separate discrete information is available for evaluation by the chief operating decision maker, or decision-making group, in deciding how to allocate resources and in assessing performance. The Company considers its chief executive officer, or CEO, as its chief operating decision maker. The Company and the CEO view the Company's operations and manages its business in one operating segment operating exclusively in the United States.

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 March 31, 2020 and December 31, 2019 were carried at fair value, determined according to the fair value hierarchy. See Note 4 for further discussion.

The carrying amounts reflected in the consolidated balance sheets for accounts payable and accrued expenses approximate their fair values due to their short-term maturities at March 31, 2020 and December 31, 2019, 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. 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:

	March 31,	
	2020	2019
Stock options	4,058,347	3,708,819
Restricted stock units	118,662	—
Potential common shares	4,177,009	3,708,819

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 April 2012, the Jump-Start Our Business Startups Act (the “JOBS Act”) was signed into law. The JOBS Act contains provisions that, among other things, reduce certain reporting requirements for an “emerging growth company.” As an emerging growth company, the Company elected to not take advantage of the extended transition period afforded by the JOBS Act for the implementation of new or revised accounting standards, and as a result, will comply with new or revised accounting standards on the relevant dates on which adoption of such standards is required for non-emerging growth companies.

In June 2016, the FASB issued ASU 2016-13, Financial Instruments-Credit Losses-Measurement of Credit Losses on Financial Instruments, or ASU 2016-13. ASU 2016-13 requires the measurement and recognition of expected credit losses for financial assets held at amortized cost. ASU 2016-13 replaces the existing incurred loss impairment model with an expected loss methodology, which will result in more timely recognition of credit losses. ASU 2016-13 is effective for the Company for annual and interim reporting periods beginning after December 15, 2022.

Effective January 1, 2019 the Company adopted FASB ASU 2016-02, Leases (Topic 842), or ASU 2016-02. ASU 2016-02 requires lessees to recognize a right-of-use, or ROU, asset and lease liability for most lease arrangements. The new standard is effective for annual reporting periods beginning after December 15, 2018. The original guidance required application on a modified retrospective basis with the earliest period presented. In August 2018, the FASB issued ASU 2018-11, Targeted Improvements to ASC 842, which included an option to not restate comparative periods in transition and elect to use the effective date of ASC 842, as the date of initial application of transition, which the Company has elected. In addition, the Company elected the package of practical expedients permitted under the transition guidance within the new standard which allowed us to carry forward the historical lease classification. As a result of the adoption of ASC 842 on January 1, 2019, the Company recorded both an operating lease right-of-use asset of \$3,265 and a lease liability of \$3,636. Additional information and disclosures required by this new standard are contained in Note 5, Right Of Use Asset and Lease Liability.

In 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 are currently assessing the impact of this standard on our financial condition and results of operations.

3. Accrued Expenses

Accrued expenses consisted of the following:

	March 31, 2020	December 31, 2019
Research and development costs	\$ 7,147	\$ 8,059
Professional fees	1,613	1,439
Payroll related	2,370	3,655
Other	147	377
Accrued expenses	<u>\$ 11,277</u>	<u>\$ 13,530</u>

4. Fair Value of Financial Assets and Liabilities

As of March 31, 2020 and December 31, 2019, the carrying amount of cash and cash equivalents and short-term investments was \$257,424 and \$292,459, respectively, which approximates fair value. Cash and cash equivalents and short-term investments includes investments in 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 March 31, 2020 using:			Total
	Level 1	Level 2	Level 3	
Assets:				
Cash Equivalents:				
Money Market Funds	\$ 51,714	\$ —	\$ —	\$ 51,714
Marketable Securities:				
Corporate Debt Securities and Commercial Paper	—	201,648	—	201,648
Total	<u>\$ 51,714</u>	<u>\$ 201,648</u>	<u>\$ —</u>	<u>\$ 253,362</u>
	Fair value Measurements as of December 31, 2019 using:			Total
	Level 1	Level 2	Level 3	
Assets:				
Cash Equivalents:				
Corporate Debt Securities and Commercial Paper	\$ —	\$ 8,885	\$ —	\$ 8,885
Money Market Funds	53,014	—	—	53,014
Marketable Securities:				
Corporate Debt Securities and Commercial Paper	—	230,165	—	230,165
Total	<u>\$ 53,014</u>	<u>\$ 239,050</u>	<u>\$ —</u>	<u>\$ 292,064</u>

Marketable Securities

The following tables summarize the Company's marketable securities:

	March 31, 2020			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Assets				
Corporate debt securities and commercial paper (due within 1 year)	\$ 201,575	\$ 348	\$ (275)	\$ 201,648
	<u>\$ 201,575</u>	<u>\$ 348</u>	<u>\$ (275)</u>	<u>\$ 201,648</u>
	December 31, 2019			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Assets				
Corporate debt securities and commercial paper (due within 1 year)	\$ 230,155	\$ 54	\$ (44)	\$ 230,165
	<u>\$ 230,155</u>	<u>\$ 54</u>	<u>\$ (44)</u>	<u>\$ 230,165</u>

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 5.25 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 March 31, 2020, the Company has not entered into any lease arrangements classified as a finance lease.

Under ASC 842, the Company determines, at the inception of the contract, whether the contract is or contains a lease based on whether the contract provides the Company the right to control the use of a physically distinct asset or substantially all of the capacity of an asset. Leases with an initial noncancelable term of twelve months or less that do not include an option to purchase the underlying asset that the Company is reasonably certain to exercise are classified as short-term leases. The Company has elected as an accounting policy to exclude from the consolidated balance sheets a right of use asset and lease liability for short-term leases.

Upon adoption of ASC 842, the Company elected the transition relief package, permitted within the standard, pursuant to which the Company did not reassess the classification of existing leases, whether any expired or existing contracts contain a lease, and whether existing leases have any initial direct costs. The Company also elected the practical expedient of not separating lease components from non-lease components for all leases. There was no cumulative-effective adjustment to the opening balance of retained earnings. The Company reviews all material contracts for embedded leases to determine if they have a right-of-use asset.

The Company recognizes rent expense on a straight-line basis over the lease period. The depreciable life of assets and leasehold improvement are limited by the expected lease term, unless there is a transfer of title or purchase option reasonably certain of exercise.

As a result of the adoption of ASC 842 on January 1, 2019, the Company recorded both an operating lease right-of-use asset of \$3,265 and a lease liability of \$3,636. The standard did not materially impact the consolidated statement of cash flows and had no impact on the consolidated statement of operations.

The Company's office lease includes both lease and non-lease components. Non-lease components relate to real estate taxes, insurance, operating expenses and common area maintenance, which are usually billed at actual amounts incurred proportionate to the Company's rented square feet of the building. These non-lease components are expensed by the Company as they are incurred and are not included in the measurement of the lease liability.

The Company's corporate headquarters is located in Boston, Massachusetts. This facility houses the Company's research, clinical, regulatory, commercial and administrative personnel. In August 2018, the Company amended its existing lease agreement and the new lease term commenced May 2019 and has a term of six years with a five-year renewal option to extend the lease. As of January 1, 2019, the Company has not included the five-year renewal option to extend the lease in its measurement of the ROU asset or lease liability. Rent expense, or operating lease costs, for the three months ended March 31, 2020 and 2019, was \$138 and \$177, respectively.

Supplemental cash flow information related to the Company's lease for the three months ended March 31, 2020, includes cash payments of \$195 used in the measurement of its operating lease liability.

The following table presents the maturities of the Company's operating lease liability related to office space as of March 31, 2020, all of which is under a non-cancellable operating lease:

	<u>Operating Lease</u>
Remainder of 2020	\$ 591
2021	802
2022	818
2023	834
2024	851
Thereafter	502
Total operating lease payments	<u>4,398</u>
Less: imputed interest	952
Total operating lease liability	<u>\$ 3,446</u>

6. Common Stock

On October 18, 2019 the Company completed a public offering of 9,324,324 shares of common stock at an offering price of \$18.50 per share, which included the exercise in full by the underwriters of their option to purchase up to 1,216,216 additional shares of common stock. The Company received net proceeds of \$161,352 after deducting underwriting discounts, commissions and offering expenses.

On January 6, 2020, the Company announced that Keith Gottesdiener, M.D., the Company's Chief Executive Officer and President, will step down from his roles with the Company. Dr. Gottesdiener stepped down from his roles as CEO, President and member of the Board of Directors following the submission of the Company's NDA filing on March 27, 2020.

In connection with the above announcement, the Company and Dr. Gottesdiener entered into a separation agreement which entitles Dr. Gottesdiener to certain severance payments and benefits as set forth therein. 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 three months ended March 31, 2020.

As of March 31, 2020, an aggregate of 8,633,042 shares of common stock were reserved for future issuance under our stock plans, including outstanding stock options and restricted stock units to purchase 7,620,670 shares of common stock and 1,012,372 shares available for future grant under our 2017 Employee Stock Purchase Plan.

7. Related-Party Transactions

Expenses paid directly to consultants and vendors considered to be related parties amounted to \$860 and \$596 for the three months ended March 31, 2020 and 2019, respectively. Outstanding payments due to these related parties as of March 31, 2020 and December 31, 2019 were \$237 and \$264, 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; our ability to negotiate our collaboration agreements, if needed; our marketing, commercial sales, and revenue generation; expectations surrounding our manufacturing arrangements; the impact of the 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 late-stage biopharmaceutical company focused on the development and commercialization of therapeutics for the treatment of rare genetic disorders which are characterized by early-onset, severe obesity and an insatiable hunger or hyperphagia. Our lead product candidate is setmelanotide, a potent melanocortin-4 receptor, or MC4R, agonist for the treatment of rare genetic disorders of obesity. We believe setmelanotide, 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.

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

We recently reported positive topline Phase 3 data in POMC deficiency obesity and LEPR deficiency obesity, and have previously demonstrated proof of concept in Phase 2 clinical trials in BBS and Alström syndrome. In these four genetic disorders of extreme and unrelenting appetite and obesity, setmelanotide has dramatically reduced both weight and hunger. The U.S. Food and Drug Administration, or the FDA, has acknowledged the importance of these results by giving setmelanotide Breakthrough Therapy designation for the treatment of obesity associated with genetic defects upstream of the MC4R in the leptin melanocortin pathways. The Breakthrough Therapy designation currently covers indications for POMC deficiency obesity, LEPR deficiency obesity, BBS and Alström syndrome. We submitted a new drug application,

or NDA, for setmelanotide for the treatment of POMC deficiency obesity and LEPR deficiency obesity on March 27, 2020.

We have demonstrated proof of concept in our Phase 2 clinical trial in BBS and Alström syndrome, and met with the FDA in May 2018 to discuss a combined pivotal Phase 3 clinical trial in these indications. Based on these discussions with the FDA, we initiated this Phase 3 trial in December 2018 and we completed enrollment in December 2019 and expect to report topline data at the end of 2020 or early in the first quarter of 2021. We have ongoing Phase 2 clinical trials, referred to as our Basket Study, in MC4R pathway heterozygous deficiency obesity and POMC epigenetic disorders, which we expanded in the second half of 2019 to include the following additional indications: SRC1 deficiency obesity, SH2B1 deficiency obesity, MC4R deficiency obesity and Smith-Magenis syndrome. We reported preliminary results in MC4R pathway heterozygous deficiency obesity in March 2019 and expect to report additional data in this indication in 2020. We also plan to report additional data from one or more of the other Basket Study indications in 2020. In total, approximately 450 obese subjects and patients have been treated with setmelanotide in previous and ongoing clinical trials in which setmelanotide demonstrated statistically significant weight loss with good tolerability.

We have acquired exclusive, worldwide rights from Takeda Pharmaceutical Company Limited, or Takeda, to develop and commercialize T-3525770, now RM-853. RM-853 is a potent, orally available ghrelin o-acyltransferase inhibitor currently in preclinical development for Prader-Willi Syndrome, or PWS. PWS is a rare genetic disorder that results in hyperphagia and early-onset, life-threatening obesity, for which there are no approved therapeutic options. We have assumed sole responsibility for the global product development and commercialization of RM-853. Takeda received an upfront fee of \$4.4 million in shares of our common stock, and will receive back-end development milestones, and single-digit royalties on future RM-853 sales. We expect to file an investigational new drug application for RM-853 in 2020.

We currently have 70 employees. Of these employees, 45 are engaged in research and development activities, 11 are engaged in pre-commercialization activities and 14 are engaged in support administration, including finance, IT and human resources. In the near-term, we expect to expand our research, clinical development and commercial personnel, in particular, and will incur increased expenses as a result. We also leverage skilled experts, consultants, contract research organizations, or CROs, and contractors to assist in managing our research and development operations under the leadership and direction of our management.

Our operations to date have been limited primarily to conducting research and development activities for setmelanotide. To date, we have not generated any product revenue and have financed our operations primarily through the proceeds received from the sales of common and preferred stock as well as capital contributions from the former parent company, Rhythm Holdings LLC, or the LLC entity. Since our initial public offering, or IPO, on October 10, 2017 through our October 18, 2019 public offering, we have raised aggregate gross proceeds of our common stock of approximately \$484.5 million before deducting underwriting discounts, commissions and offering related transaction costs. We will not generate revenue from product sales until we successfully complete development and obtain regulatory approval for setmelanotide, which we expect will take a number of years and is subject to significant uncertainty. 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 March 31, 2020 we had an accumulated deficit of \$359.5 million. Our net losses were \$34.2 million and \$29.0 million for the three months ended March 31, 2020 and 2019, respectively. We expect to continue to incur significant expenses and increasing operating losses over the foreseeable future. We expect our expenses will increase substantially in connection with our ongoing activities, as we:

- continue to conduct clinical trials for setmelanotide;
- engage contract manufacturing organizations, or CMOs, for the manufacture of setmelanotide for clinical trials and the manufacture of RM-853 for preclinical development;

- seek regulatory approval for setmelanotide;
- expand our clinical and financial operations and build a marketing and commercialization infrastructure; and
- operate as a public company.

As of March 31, 2020, our existing cash and cash equivalents and short-term investments were approximately \$257.4 million. We expect that our existing cash and cash equivalents and short-term investments will enable us to fund our operating expenses through at least the end of 2021.

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. Prior to our organization and a corporate reorganization, we were part of Rhythm Pharmaceuticals, Inc., a Delaware corporation which was organized in November 2008 and which commenced active operations in 2010. We refer to this corporation as the Predecessor Company.

Impact of Novel Coronavirus

We are closely monitoring how the spread of COVID-19 is affecting our employees, business, preclinical studies and clinical trials. In response to the COVID-19 pandemic, we have closed our executive offices with all employees continuing their work outside of our offices and travel has been restricted. We currently continue to expect to meet disclosed timelines for reporting data from our pivotal Phase 3 trial in BBS and Alström syndrome and our Basket Study. We are continuing our regular interactions with the FDA and EMA and based on current information, we do not anticipate COVID-19 to materially affect our regulatory timelines for POMC deficiency obesity or LEPR deficiency obesity. We do not currently anticipate any disruption in the clinical supply of setmelanotide and our CMOs have indicated that they have appropriate plans and procedures in place to ensure uninterrupted future supply of clinical and commercial-grade setmelanotide, subject to potential limitations on their operations due to COVID-19. As a result, we do not currently expect that the COVID-19 pandemic will have a material impact on our business, results of operations and financial condition. At this time, however, there is significant uncertainty relating to the trajectory of the pandemic and the impact of related responses, and disruptions caused by the COVID-19 pandemic may 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. The impact of COVID-19 on our future results will largely depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as the ultimate geographic spread of the disease, the duration of the pandemic, travel restrictions and social distancing in the United States and other countries, business closures or business disruptions, the ultimate impact on financial markets and the global economy, and the effectiveness of actions taken in the United States and other countries to contain and treat the disease. See “Risk Factors—The outbreak of the novel coronavirus disease, COVID-19, could 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 any revenue from product sales and do not expect to generate any revenue from the sale of setmelanotide unless and until we receive regulatory approval of setmelanotide. We cannot predict if, when, or to what extent we will generate revenues from the commercialization and sale of setmelanotide. Setmelanotide is currently our most advanced product candidate in clinical development, and we may never succeed in achieving regulatory approval for setmelanotide or any other product candidate that we decide to pursue in the future.

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 and RM-853, 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	
	March 31,	
	2020	2019
Research and development expense	\$ 22,504	\$ 22,761

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 RM-853 development programs progress. However, we do not believe that it is possible at this time to accurately project total program-specific expenses to commercialization and there can be no guarantee that we can meet the funding needs associated with these expenses.

Selling, general and administrative expenses

Selling expenses consist of professional fees related to preparation for the eventual commercialization of setmelanotide, if approved, as well as salaries and related benefits for commercial employees, including stock-based compensation. As we accelerate our preparation for commercialization and, if it is approved, 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	
	March 31,	
	2020	2019
Selling, general and administrative expense	\$ 12,796	\$ 7,759

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

Critical Accounting Policies and Estimates

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

During the three months ended March 31, 2020, there were no significant changes to our critical accounting policies as reported in our Annual Report on Form 10-K for the fiscal year ended December 31, 2019.

Results of Operations

Comparison of the three months ended March 31, 2020 and 2019

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

	Three Months Ended		Change	
	2020	2019	\$	%
(in thousands)				
Statement of Operations Data:				
Operating Expenses:				
Research and development	\$ 22,504	\$ 22,761	\$ (257)	(1)%
Selling, general, and administrative	12,796	7,759	5,037	65 %
Total operating expenses	35,300	30,520	4,780	16 %
Loss from operations	(35,300)	(30,520)	(4,780)	16 %
Other income, net	1,136	1,546	(410)	(27)%
Net loss	\$ (34,164)	\$ (28,974)	\$ (5,190)	18 %

Research and development expense. Research and development expense decreased by \$0.3 million to \$22.5 million in 2020 from \$22.8 million in 2019, a decrease of 1%. The decrease was primarily due to the following:

- a decrease of \$2.7 million related to our clinical trial associated with the GO-ID genotyping study. This study is nearing its completion and we have begun to gather and analyze the results from the study; and
- a decrease of \$1.2 million related to genetic sequencing efforts, as the near-completion of the GO-ID study resulted in lower sequencing volume.

The above decreases were partially offset by:

- an increase of \$1.0 million related to consulting services to assist in the submission of our NDA to the FDA on March 27, 2020;
- an increase of \$0.9 million related to our clinical trials associated with setmelanotide. We continue to expand the Phase 2 basket study, our long-term extension study and the Phase II study of a weekly formulation of setmelanotide;
- an increase of \$0.9 million primarily related to the manufacturing of setmelanotide API for clinical trials and commercial supply; and
- an increase of \$0.6 million due to the hiring of additional personnel related to community building and education efforts for physicians, care providers and patients who are facing rare genetic disorders of obesity.

Selling, general and administrative expense. Selling, general and administrative expense increased by \$5.0 million to \$12.8 million in 2020 from \$7.8 million in 2019, an increase of 65%. The increase was primarily due to the following:

- a charge of \$3.5 million related to the separation agreement and modification of stock options for our former chief executive officer upon his departure on March 27, 2020; and
- an increase of \$1.2 million related to efforts to drive patient engagement and disease awareness about rare genetic causes of obesity and prepare for the potential commercialization of setmelanotide in the U.S.

Net loss. Net loss increased by \$5.2 million to \$34.2 million in 2020, from \$29.0 million in 2019. The increase in net loss was primarily due to the increase in selling, general and administrative expenses discussed above.

Liquidity and Capital Resources

As of March 31, 2020, our cash and cash equivalents and short-term investments were approximately \$257.4 million.

Cash flows

The following table provides information regarding our cash flows for the three months ended March 31, 2020 and 2019:

	Three Months Ended March 31,	
	2020	2019
	(in thousands)	
Net cash provided by (used in):		
Operating activities	\$ (36,098)	\$ (31,378)
Investing activities	28,873	23,541
Financing activities	707	316
Net increase in cash, cash equivalents and restricted cash	<u>\$ (6,518)</u>	<u>(7,521)</u>

Net cash used in operating activities

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

Net cash used in operating activities was \$36.1 million for the three months ended March 31, 2020 and consisted primarily of a net loss of \$28.6 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 \$7.5 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 operating activities was \$31.4 million for the three months ended March 31, 2019 and consisted primarily of a net loss of \$26.0 million adjusted for non-cash items, which consisted of non-cash stock-based compensation, depreciation and amortization and rent expense. The change in operating assets and liabilities reflected a total use of cash of approximately \$5.4 million for an increase in prepaid expenses associated with our CROs and timing of payments for the decrease in accounts payables.

Net cash provided by investing activities

Net cash provided by investing activities for the three months ended March 31, 2020 relates to the net maturities of short-term investments.

Net cash provided by investing activities for the three months ended March 31, 2019 relates to the net purchases of short-term investments of \$24.4 million, partially offset by \$0.8 million of cash used for tenant improvements related to our new office space.

Net cash provided by financing activities

Net cash provided by financing activities was \$0.7 million for the three months ended March 31, 2020, which represents net proceeds from purchases made under our 2017 Employee Stock Purchase Plan and proceeds from the exercise of stock options.

Net cash provided by financing activities was \$0.3 million for the three months ended March 31, 2019, which represents net proceeds from purchases made under our 2017 Employee Stock Purchase Plan 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. In addition, if we obtain marketing approval for setmelanotide, 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 through at least the end of 2021. 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 scope, progress, results and costs of clinical trials for our setmelanotide program;
- the costs, timing and outcome of regulatory review of our setmelanotide program;
- the costs to commercialize setmelanotide, if approved, by building an internal sales force or entering into collaborations with third parties and providing support services for patients;
- 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; and
- our ability to establish and maintain additional collaborations on favorable terms, if at all.

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 marketing approval and achieve product sales. In addition, setmelanotide, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of setmelanotide following regulatory approval, if at all. 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 on Form 10-Q as this continues to evolve globally. See “Impact of Novel Coronavirus” above and “Risk Factors— The outbreak of the novel coronavirus disease, COVID-19, could 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 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. From August 2015 through August 2017, we raised aggregate gross proceeds of \$81.0 million through our issuance of series A preferred stock. Since our IPO, in October 2017, through our October 2019 public offering, we have raised aggregate net proceeds of approximately \$450.0 million through the issuance of our common stock after deducting underwriting discounts, commissions and offering related transaction costs.

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

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

Contractual obligations

As of March 31, 2020, 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, 2019.

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 March 31, 2020, 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, 2019.

Item 4. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

In connection with the preparation of this Quarterly Report on Form 10-Q, our management completed an evaluation, as of March 31, 2020, with the participation of our principal executive officer and principal financial officer, as to the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act).

It should be noted that any system of controls, however well designed and operated, can provide only reasonable, and not absolute, assurance that the objectives of the system will be met. In addition, the design of disclosure controls and procedures must reflect the fact that there are resource constraints and that management is required to apply judgment in evaluating the benefits of possible controls and procedures relative to their costs. Based upon the evaluation, our principal executive officer and principal financial officer have concluded that, as of March 31, 2020, 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 period covered by this report 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 late-stage biopharmaceutical company with a limited operating history and have not generated any revenue from product sales. We have incurred significant operating losses since our inception, anticipate that we will incur continued losses for the foreseeable future and may never achieve profitability.

We are a late-stage biopharmaceutical company with a limited operating history on which to base your investment decision. Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. We were incorporated in February 2013. Our operations to date have been limited primarily to acquiring rights to intellectual property, business planning, raising capital, developing our technology, identifying potential product candidates, undertaking preclinical studies and conducting research and development activities, including clinical trials, for setmelanotide. We have never generated any revenue from product sales. We have not obtained any regulatory approvals for setmelanotide.

Since our inception, we have focused substantially all of our efforts and financial resources on the research and development of setmelanotide, which is currently in Phase 3 clinical development for four indications, POMC deficiency obesity, LEPR deficiency obesity, Bardet-Biedl syndrome, or BBS, and Alström syndrome and in Phase 2 clinical development for other indications. We have funded our operations to date primarily through the proceeds from the sales of common stock and preferred stock as well as capital contributions from our former parent, Rhythm Holdings LLC, or the LLC entity, and have incurred losses in each year since our inception. See “Part I, Item 2. Management’s Discussion and Analysis of Financial Condition and Results of Operations—Corporate Background.”

Our net loss and comprehensive losses were \$34.2 million and \$29.0 million for the three months ended March 31, 2020 and 2019, respectively. As of March 31, 2020, we had an accumulated deficit of \$359.5 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, if we obtain marketing approval for setmelanotide, we will incur significant sales, marketing and outsourced manufacturing expenses. We will incur costs associated with operating as a public company. As a result, we expect to continue to incur significant and increasing operating losses for the foreseeable future. Because of the numerous risks and uncertainties associated with developing pharmaceutical products, we are unable to predict the extent of any future losses or when we will become profitable, if at all. Even if we do become profitable, we may not be able to sustain or increase our profitability on a quarterly or annual basis.

Our ability to become profitable depends upon our ability to generate revenue. To date, we have not generated any revenue from setmelanotide, and we do not know when, or if, we will generate any revenue. We do not expect to generate significant revenue unless and until we obtain marketing approval for, and begin to sell, setmelanotide. Our ability to generate revenue depends on a number of factors, including, but not limited to, our ability to:

- 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;
- successfully manufacture or contract with others to manufacture setmelanotide;
- ensure setmelanotide is available to patients with rare genetic disorders of obesity;
- commercialize setmelanotide, if approved, by building an internal sales force or entering into collaborations with third parties; and
- achieve market acceptance of setmelanotide in the medical community and with third-party payors.

Absent our entering into collaboration or partnership agreements, we expect to incur significant sales and marketing costs as we prepare to commercialize setmelanotide. Even if we successfully complete our pivotal clinical trials and setmelanotide is approved for commercial sale, and we incur the costs associated with these activities, 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 advancing setmelanotide through clinical development. 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 clinical trials. We intend to use our available cash resources primarily for the clinical development and regulatory approval of setmelanotide. Depending on the status of regulatory approval and, if approved, commercialization of setmelanotide, as well as the progress we make in the sale of setmelanotide, 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 gross proceeds of \$81.0 million through our issuance of series A preferred stock. Since our initial public offering, or IPO, through our October 18, 2019 public offering, we have raised aggregate net proceeds of approximately \$450.0 million through the issuance of our common stock after deducting underwriting discounts, commissions and estimated offering related transaction costs. As of March 31, 2020, our cash and cash equivalents and short-term investments were approximately \$257.4 million. We expect our existing cash and cash equivalents and short-term investments will enable us to fund our operating expenses through at least the end of 2021. 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 regulatory approval for, and to commercialize, setmelanotide. Raising funds in the current economic environment, particularly in light of the economic downturn and 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.

Our very limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

We were incorporated in February 2013 and 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 clinical trials. We have not yet demonstrated our ability to successfully complete a pivotal Phase 3 clinical trial, obtain marketing approvals, 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.

In addition, as a relatively new business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. 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 expect our financial condition and operating results to continue to fluctuate significantly from quarter-to-quarter and year-to-year due to a variety of factors, many of which are beyond our control. Accordingly, you should not rely upon the results of any quarterly or annual periods as indications of future operating performance.

Our historical financial information may not be a reliable indicator of our future results.

The historical financial information we have included in this Quarterly Report on Form 10-Q may not reflect our future results of operations, financial position and cash flows because our historical financial information does not reflect changes that we have incurred and expect to continue to incur as we transition to a commercial company including changes in cost structure, personnel needs, financing and operations of our business. In addition, our financial results may vary from quarter to quarter and from year to year in response to a variety of factors beyond our control. As a result, it may be

difficult for investors to compare our future results to historical results or to evaluate our relative performance or trends in our business.

Risks Related to the Development of Setmelanotide

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

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

From time to time, we may also disclose interim data from our preclinical studies and clinical trials. 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 U.S. Food and Drug Administration, or FDA, and the European Medicines Agency, or EMA, may disagree with our interpretation of clinical results obtained from our Phase 3 clinical trials for POMC and LEPR deficiency obesities, our results do not guarantee that the New Drug Application, or NDA, we have submitted will be filed for substantive review or will support regulatory approval, and, even if our Phase 3 data are deemed to be positive by the FDA or EMA, the FDA or EMA may disagree with other aspects of the NDA or planned Marketing Authorization Application, or MAA, submission and, as a result, the FDA or the European Commission may decline to approve setmelanotide for the proposed indications.

We have reported positive topline data from our Phase 3 clinical trials for POMC and LEPR deficiency obesities. However, even if we believe that the data from the trial are positive, the FDA or EMA could determine that the data from such trials were negative or inconclusive, not sufficiently meaningful from a clinical perspective or could reach different conclusions than we have on the same data. Negative or inconclusive results of a clinical trial or a difference of opinion could cause the FDA or the European Commission to decline to approve our applications or cause the FDA or EMA to require us to repeat the trial or conduct additional clinical trials prior to obtaining approval for commercialization, and there is no guarantee that additional trials would achieve positive results to the satisfaction of the FDA or EMA or that the FDA or EMA will agree with our interpretation of the results. Any such determination by the FDA or EMA would delay

the timing of our commercialization plan for setmelanotide or prevent its further development, and adversely affect our business operations. Additionally, the FDA or EMA may not accept our NDA for review and may provide commentary at any time during the review process which could require us to submit additional information and delay the review timeline, adversely affect the review process, or even prevent the approval of setmelanotide, any of which would adversely affect our business. We may not be able to appropriately remedy issues that the FDA or EMA may raise in its review of our NDA submission or equivalent EU submission, and we may not have sufficient time or financial resources to conduct future activities to remediate issues raised by the FDA or EMA.

There is no guarantee that the data obtained from our Phase 3 clinical trials for POMC and LEPR deficiency obesities will be supportive of, or guarantee, a successful NDA or MAA submission, or result in our obtaining FDA or the European Commission's approval of setmelanotide in a timely fashion and for a commercially viable indication, or at all. For example, the FDA or EMA could determine that the trials did not meet their objectives or the FDA or EMA could still have concerns regarding the conduct of the Phase 3 trials. At any future point in time, the FDA or EMA could require us to complete further clinical or preclinical trials, or take other actions which could delay or preclude any NDA submission or approval of the NDA or MAA and could require us to obtain significant additional funding. There is no guarantee such funding would be available to us on favorable terms, if at all, nor is there any guarantee that FDA or EMA would consider any additional information complete or sufficient to support approval. Following any NDA submission, the FDA may hold an advisory committee meeting to obtain committee input on the safety and efficacy of setmelanotide. Typically, advisory committees will provide responses to specific questions asked by the FDA, including the committee's view on the approvability of the product candidate under review. Advisory committee decisions are not binding but an adverse decision at the advisory committee may have a negative impact on the regulatory review of setmelanotide. Additionally, we may choose to engage in the dispute resolution process with the FDA if we do not receive approval, which could extend the timeline for any potential approval.

There is no assurance that our planned submission with the EMA will be submitted within the timeframes we expect. Further, there is no guarantee that the data included in any regulatory submissions will be deemed sufficient by the FDA or EMA for approval. There is no guarantee that the FDA or EMA will deem our trial protocols or results from the study sufficient when they are formally reviewed as a part of an NDA or EU equivalent submission even though we discussed the design of the trials with FDA and EMA prior to commencing the trials. The FDA and EMA each have significant discretion in the review process, and we cannot predict whether the FDA or EMA will agree with our conclusions regarding the results of the Phase 3 trials, including whether our data are reliable and generalizable.

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

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

Positive results from any of our Phase 1 and Phase 2 clinical trials of setmelanotide, or initial results from our Phase 3 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 current 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. 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 proof of concept in Phase 2 clinical trials in POMC deficiency obesity, LEPR deficiency obesity, BBS and Alström syndrome, four genetic disorders of extreme and unrelenting appetite and obesity, in which setmelanotide

dramatically reduced both weight and hunger. We have also reported positive topline results from our pivotal Phase 3 clinical trials in POMC deficiency obesity and LEPR deficiency obesity, which demonstrated a clinically meaningful impact on reductions of weight and hunger. 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 have and will continue to have multiple clinical trials of setmelanotide ongoing, which are designed to include multiple genetically and clinically defined populations under one investigational protocol, although each population is enrolled and analyzed separately. A “basket” trial design could potentially decrease the time to study new populations by decreasing administrative burden. However, these trials may not provide opportunities for acceleration and do not overcome limitations to extrapolating data from the experience in one disease to other diseases, because safety and efficacy results in each indication are analyzed separately. Accordingly, clinical success in a basket trial, or any trial in one indication, may not predict success in another indication. In contrast, in the event of an adverse safety issue, clinical hold, or other adverse finding in one or more indications being tested, such event could adversely affect our trials in the other indications and may delay or prevent completion of the clinical trials.

Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in later stage clinical trials after achieving positive results in early stage development, and we cannot be certain that we will not face similar setbacks. These setbacks have been caused by, among other things, pre-clinical findings made while clinical trials were underway. However, we have completed the key toxicology studies that the FDA will require for our first NDA submission, and which we believe outlines the studies the EMA will require for MAA submission, which include, among others, chronic toxicity studies, reproductive and developmental toxicity studies, and juvenile toxicology studies. Based on the totality of animal testing results to date, including the lack of any observed genotoxicity or tissue proliferative activity of setmelanotide in chronic toxicity studies, the FDA has agreed to permit us to defer carcinogenicity studies until after approval of an NDA for setmelanotide. While we may submit carcinogenicity study results in the NDA submission to support regulatory approval, we may decide to defer the submission of all carcinogenicity studies until after we receive regulatory approval to market setmelanotide in the United States.

In June 2018, setmelanotide was designated as PRiority MEDicine, or PRIME, by the EMA’s Committee for Medicinal Products for Human Use, or 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 European Union, or EU. As part of this designation, the EMA has provided guidance to us concerning the development of setmelanotide. The EMA advised us that we should include the mouse carcinogenicity study in our initial filing for marketing authorization in the EU. We cannot be certain how long it will take to complete the mouse carcinogenicity study required to be included in our application for marketing authorization, and this could delay the timing of submission of a potential marketing authorization in the EU. The EMA also advised us that it will not require the rat carcinogenicity study until post approval. However, the EMA does not provide as firm guidance as the FDA, and accordingly, there can be no guarantee that we will be able to achieve this deferral of the rat carcinogenicity study, which could impact the timing of grant of any potential marketing authorization in the EU.

In addition, the FDA has requested that in our chronic rat and monkey studies we re-assess certain cells in brain, renal and liver tissues for the presence of vacuoles, which are common membrane-bound compartments. The recommendation was based on the FDA’s review of a summary of a monkey study that noted the presence of macrophage aggregates, which are groupings of specific white blood cells, in the choroid plexus, a network of blood vessels and epithelial tissue in the membrane lining outside the brain and spinal cord. The FDA noted that the existence of macrophage aggregates appears to be related to the polyethylene glycol, or PEG, vehicle in the product, rather than setmelanotide itself. A similar question was raised by the competent authorities in France, in connection with the use of PEG in products for younger pediatric indications, and in discussion of our Pediatric Investigational Plan, or PIP. Based on this, we performed this re-assessment, which confirmed that no additional findings were present in any monkey tissues, but which did find a very small number of rats with vacuolated epithelial cells, or brain surface lining cells, in the choroid plexus of minimal severity that also appeared to be related to the PEG vehicle. We do not believe these findings raise any important safety

concerns, in part because of the minimal severity, the localization of these aggregates, the lack of any adverse histopathological changes, and the lack of findings in other tissues.

However, neither the FDA nor regulatory agencies in the EU have indicated whether they agree with our position. In addition, the EMA has requested additional preclinical mechanistic studies to better understand these findings. It is also possible that regulatory agencies may require us to reflect these findings in the toxicological portion of the product labeling, and this may delay study in the youngest pediatric patients in some EU member states, such as France. By a decision on June 15, 2018, the EMA agreed with the PIP for setmelanotide and granted a related deferral. We are required to complete all of the studies included in the PIP by December 2024.

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

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 13,567 patients, as of September 2019, 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 clinical epidemiology, we have estimated the potential addressable patient populations with these MC4R pathway deficiencies based on the following sources and assumptions:

- *POMC Deficiency Obesity.* Our addressable patient population estimate for POMC deficiency obesity is approximately 100 to 500 patients in the United States, with a comparable addressable patient population in Europe. Our estimates are based on:
 - approximately 50 patients with POMC deficiency obesity noted in a series of published case reports, each mostly reporting a single or small number of patients. However, we believe our addressable patient population for this deficiency may be approximately 100 to 500 patients in the United States, and a comparable addressable patient population in Europe, as most of the reported cases are from a small number of academic research centers, and because genetic testing for POMC deficiency obesity is often unavailable and currently is rarely performed;
 - our belief, based on discussions with experts in rare diseases, that the number of diagnosed cases could increase several-fold with increased awareness of this deficiency and the availability of new treatments;
 - U.S. Census Bureau figures for adults and children, and Centers for Disease Control and Prevention, or CDC, prevalence numbers for severe adult obese patients (body mass index, or BMI, greater than 40 kg/ m²) and for early onset, severe 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 proprotein convertase subtilisin/kexin 1, or PCSK1, gene disorders) of approximately 0.06%.

- *LEPR Deficiency Obesity.* 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 Centers for Disease Control and Prevention, or CDC, prevalence numbers for severe adult obese patients (body mass index, or BMI, greater than 40 kg/ m²) and for early onset, severe obese children (99th percentile at ages two to 17 years old);
 - with wider availability of genetic testing expected for LEPR deficiency obesity and increased awareness of new treatments, our belief that up to 40% of patients with these disorders may eventually be diagnosed; and
 - our internal sequencing yield for LEPR deficiency obesity patients of approximately 0.15%.

Using these sources and assumptions, we calculated our estimates for addressable populations by multiplying (x) our estimate of the number of patients comprised of children with severe obesity and our estimate of a projected number of adults with severe obesity who have a history of early onset obesity, (y) the estimated prevalence from epidemiology studies of approximately 1% for LEPR deficiency obesity, and (z) our estimated diagnosis rate of up to 40%. In addition, we considered the results of our internal sequencing yields, which support our clinical epidemiology estimates.

- *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 or LEPR Heterozygous Deficiency Obesities, or HET obesity.* Our addressable patient population estimate for patients with high-impact variants (the subset of POMC or LEPR heterozygous patients with loss of function variants such as truncations, frame-shift, and splice variants, as well as well-characterized, published missense variants likely to cause loss-of-function variants of the MC4R pathway, expected to be most responsive to setmelanotide) is approximately greater than 20,000 patients in the United States, with a comparable addressable patient population in Europe. Our estimates are based on:

- U.S. Census Bureau figures for adults and children, and CDC prevalence numbers for severe adult obese patients (body mass index, or BMI, greater than 40 kg/ m²) and for early onset, severe obese children (99th percentile at ages two to 17 years old); and
- our internal sequencing yield for patients with high-impact heterozygous variants of approximately 0.7%.
- *POMC Epigenetic Disorders.* There is currently no epidemiology data that defines the prevalence of POMC epigenetic disorders.
- *SRC1 Deficiency Obesity.* Our addressable patient population estimate for SRC1 deficiency obesity is approximately greater than 23,000 patients in the United States. This estimate is based on:
 - U.S. Census Bureau figures for adults and children, and CDC prevalence numbers for severe adult obese patients (body mass index, or BMI, greater than 40 kg/ m²) and for early onset, severe obese children (99th percentile at ages two to 17 years old); and
 - our internal sequencing yield for SRC1 deficiency obesity patients of approximately 2.5% prior to application of functional and computational filters.
- *SH2B1 Deficiency Obesity.* Our addressable patient population estimate for SH2B1 deficiency obesity is approximately greater than 24,000 patients in the United States. This estimate is based on:
 - U.S. Census Bureau figures for adults and children, and CDC prevalence numbers for severe adult obese patients (body mass index, or BMI, greater than 40 kg/ m²) and for early onset, severe obese children (99th percentile at ages two to 17 years old); and
 - our internal sequencing yield for SH2B1 deficiency obesity patients of approximately 1.8% prior to application of functional and computational filters.
- *MC4R Deficiency Obesity.* Our addressable patient population estimate for MC4R deficiency obesity is approximately greater than 10,000 patients in the United States. This estimate is based on:
 - U.S. Census Bureau figures for adults and children, and CDC prevalence numbers for severe adult obese patients (body mass index, or BMI, greater than 40 kg/ m²) and for early onset, severe obese children (99th percentile at ages two to 17 years old); 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 greater than 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.

We are conducting additional clinical epidemiology studies to strengthen these prevalence projections. In parallel, we have developed a patient registry for diagnosed patients with POMC deficiency and LEPR deficiency (and other genetic disorders of obesity) which might further inform prevalence projections for these rare genetic orders.

Another method to estimate the size of these ultra-rare populations by genetic epidemiology is using newly available large genomic databases, containing full genome sequencing or exome sequencing. Ultra-rare orphan diseases are generally categorized as those that affect fewer than 20 patients per million. We have begun some substantial efforts with a series of such databases and/or collaborators. Our initial work has been with a database of approximately 140,000 genomes, which is representative of the U.S. population, and suggests that genetic epidemiology estimates of POMC deficiency obesity and LEPR deficiency obesity may be five times higher than clinical epidemiology estimates. These efforts generally are based on the prevalence of heterozygous mutations, as true null mutations are ultra-rare, and then standard scientific methods such as the Hardy-Weinberg equilibrium calculations, are applied to estimate the prevalence in the U.S. population. These methods make assumptions that may not be sufficiently robust for ultra-rare genetic disorders and have the inherent variability of estimates for rare events.

Furthermore, as of September 2019, we collected samples from 13,567 individuals with severe obesity, which yielded 11.7%, or 1,584, genetically-identified individuals with a rare genetic variant of the MC4R pathway and who may be eligible for inclusion in our Phase 2 Basket Study or pivotal Phase 3 clinical trials. Inclusive of these results, our sequencing programs have now sequenced over 25,000 severely obese individuals. We plan to update results from our sequencing activity in 2020. The yields for the indications are outlined above, but then are subject to application of functional and/or computational filters to calculate the prevalence estimates in the United State population. A rarity filter means the specific variant appears in less than 1% of people, and the functional and computational filters help us focus our estimates based on the highest confidence loss-of-function variants. These genetic sequencing results have identified samples from 29 patients with POMC deficiency obesity and LEPR deficiency obesity, which is consistent with our clinical epidemiology estimates.

In addition, the databases currently available only provide limited clinical data, such as age, weight and BMI, that would be needed to associate genetic defects with severe obesity. Our continued investigations support that the genetic epidemiological estimates are larger than the clinical epidemiological estimates, but we will likely need to reconcile the scientific definition of mutations with the regulatory definition.

We believe the separate analyses that we have completed using clinical epidemiology and genetic epidemiology provide a robust range of patient population estimates for POMC and LEPR deficiency obesities. However, as the clinical epidemiology estimates tend to be lower, to be conservative, we generally reference the clinical epidemiology figures in our descriptions of our target indications.

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

If the actual number of patients suffering from each of the MC4R pathway deficiencies we are targeting is smaller than we estimate or if any approval that we obtain is based on a narrower definition of these patient populations, including pediatric populations, our ability to recruit patients to our trials may be materially adversely affected. Patient enrollment may also be adversely affected by competition and other factors.

If the actual number of patients with any of the MC4R pathway deficiencies we are targeting is lower than we believe, it may be difficult to recruit patients, and this may affect the timelines for the completion of clinical trials. If we experience delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could also be delayed or prevented.

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 this

population, and to locate and enroll pediatric patients. Additionally, it may be challenging to ensure that pediatric or adolescent patients adhere to clinical trial protocols.

We have started treating patients six years and older in our trials. Our aim is to gain regulatory approval and labeling for patients six years of age and older. We have only recently received permission from the FDA and other equivalent competent authorities in the EU member states to enroll these younger patients, aged six to eleven, in our pivotal trials. However, there may be issues that preclude the ultimate approval and labeling, if any, including, but not limited to, potential disagreement on dose titration, or delivery methods for small doses, or the suitability of patient reported outcomes in younger patients, the clinical endpoints in rapidly growing patients, as well as avoiding over-suppression of normal appetite in adolescents. In addition, the competent authorities in the EU member states may consider the PEG vehicle in the product to carry additional risks in pediatric patients, and we may look to new formulations, such as our once-weekly formulation, as being more suitable to younger pediatric patients. We also may not have one-year clinical data in six to eleven year old patients at the time of the NDA submission for POMC deficiency obesity and LEPR deficiency obesity, if we begin recruiting six to eleven year old patients into our pivotal trials, though we can provide one-year clinical data when it becomes available. We cannot predict if the FDA or the European Commission in the EU will approve and issue a marketing authorization for setmelanotide for use in younger pediatric patients, nor provide an estimate for the timing for approval, if any, for the use of setmelanotide for such patients. Furthermore, if the FDA or the European Commission in the EU do not approve or grant marketing authorization for the use of setmelanotide in this population, we will not be permitted to promote the use of setmelanotide for these patients, even if setmelanotide is approved in the United States by the FDA and authorized to be placed on the market in the EU by the European Commission for use in patients twelve and older. Even if approved, the promotion of setmelanotide for uses that are not approved by the FDA or authorized in the EU constitutes off-label promotion. The off-label promotion of medicinal products is prohibited in the United States and EU. Breach of the rules governing the promotion of medicinal products in the United States and EU are subject to administrative enforcement and judicial action, including fines and imprisonment.

While we currently have no knowledge of competitors developing product candidates intended to treat upstream MC4R pathway deficiencies, other than Prader-Willi syndrome, competitors may emerge. If that were to occur and competitors initiated clinical trials for product candidates that treat the same indications as setmelanotide, patients who would otherwise be eligible for our clinical trials may instead enroll in the clinical trials of our competitors' product candidates, and could impact our commercial success.

Patient enrollment is also affected by other factors including:

- the severity of the disease under investigation;
- the eligibility criteria for the clinical trial in question;
- the perceived risks and benefits of the product candidate under study;
- the success of efforts to facilitate timely enrollment in clinical trials;
- the patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment; and
- the proximity and availability of clinical trial sites for prospective patients.

Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays, could require us to abandon one or more clinical trials altogether and could delay or prevent our receipt of necessary regulatory approvals. Enrollment delays in our clinical trials may result in increased development costs for setmelanotide, which would cause the value of our company to decline and limit our ability to obtain additional financing.

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.

We recently announced positive topline results from pivotal Phase 3 clinical trials for setmelanotide for POMC deficiency obesity and LEPR deficiency obesity. These trials are overlapping in timing and duration and we have submitted one NDA for these two indications, which may have an impact on NDA timing and complexity.

We believe we have demonstrated proof of concept in BBS and Alström syndrome based on prior clinical data, and we completed enrollment of a combined pivotal Phase 3 clinical trial in BBS and Alström syndrome in December 2019, but enrollment of supplemental cohort continues. We believe that the combined BBS and Alström syndrome Phase 3 pivotal clinical trial design will be similar to those for POMC and LEPR deficiency obesity, respectively, but may also include differences most likely due to the larger available patient population for inclusion in a clinical study. There may be other changes as well, including simpler titration schemes, a short placebo-controlled randomized period, and modest differences in our statistical approach due to the different patient populations, the size and combined nature of the study.

We have also initiated Phase 2 clinical trials, referred to as our Basket Study, for POMC and other MC4R pathway heterozygous deficiency obesities and POMC epigenetic disorders. Based on results from our genetic sequencing programs, we expanded our Basket Study in the second half of 2019 to include SRC1 deficiency obesity, SH2B1 deficiency obesity, MC4R deficiency obesity and Smith-Magenis syndrome. We anticipate that the Basket Study may be more complex than the Phase 2 clinical trials for which we have achieved proof of concept, and will include larger numbers of subjects to be enrolled. In addition, we anticipate that we will have to define a subset of heterozygous patients for whom setmelanotide will have a clinically meaningful impact, and this may take more patients and more time to develop than other indications for setmelanotide. In March 2019, we announced data for High Impact Het patients (the subset of MC4R pathway heterozygous patients with well-characterized, published, high-impact loss-of-function variants, that we expect to be most responsive to setmelanotide). However, the data from these initial patients is limited and preliminary, and further clinical study is needed to determine if the results in this subset of patients is both robust and consistent.

In addition, the outcome for these new indications is less certain. As our genetic sequencing efforts progress, we expect to add additional new MC4R pathway indications to our Basket Study in the future, and many uncertainties will exist for these new populations as well. Therefore, we believe that a transition from proof of concept to pivotal trials will be longer and more complex for POMC heterozygous deficiency obesity, and POMC epigenetic disorders, and possibly for any additional new indications, due to the greater variety of clinical presentation in those conditions.

Successful completion of our Phase 3 clinical trials is a prerequisite to submitting an NDA to the FDA, a marketing authorization application to the EMA, and other applications for marketing authorization to equivalent competent authorities in foreign jurisdictions, and consequently, the ultimate approval and commercial marketing of setmelanotide.

We do not know whether our planned additional Phase 2 or Phase 3 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:

- the FDA or other equivalent competent authorities in foreign jurisdictions may deny permission to proceed with our ongoing or planned Phase 3 clinical 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 approvals or an additional investigational new drug application, or IND, that may be required;
- negative results from our ongoing and planned preclinical studies, or the FDA or other equivalent competent authorities in foreign jurisdictions requiring additional preclinical studies;
- delays in commencing additional necessary preclinical studies, including carcinogenicity and juvenile toxicology studies;

- 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;
- 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;
- difficulties in obtaining Institutional Review Board, or IRB, and/or ethics committee approval to conduct a clinical trial at a prospective site or sites;
- challenges in recruiting and enrolling patients to participate in clinical trials, including the size and nature of the patient population, the proximity of patients to clinical trial sites, eligibility criteria for the clinical trial, the nature of the clinical trial protocol, the availability of approved effective treatments for the relevant disease and competition from other clinical trial programs for similar indications;
- severe or unexpected drug-related side effects experienced by patients in a clinical trial, including side effects previously identified in our completed clinical trials;
- delays in identifying and recruiting patients with any of the genetic causes of obesity in indications that we are targeting;
- disagreement by the FDA, other regulatory agencies or the equivalent competent authorities in foreign jurisdictions with our clinical trial designs, which may in turn cause delays in initiating our clinical trials, or may lead to rejection of our interpretation of data from clinical trials or to changes in the requirements for approval even after it has reviewed and commented on the design for our clinical trials;
- the requirement to have a placebo controlled study even though the FDA and EMA did not impose one for POMC deficiency obesity or LEPR deficiency obesity, as we cannot be certain that this will be true for other indications or that the FDA or EMA, an advisory committee or the equivalent competent authorities in foreign jurisdictions will not change its guidance, as it has done so in the past for other open control trials;
- uncertainty related to the length of placebo-controlled intervals in clinical trials;
- the need to perform non-inferiority trials, which can be larger, longer and more costly, if treatment is approved for similar indications;
- potential delays in the enrollment for our clinical trials of BBS and Alström syndrome (or any new indications we may study) for many reasons, including the fact that while we may have additional discussions with the FDA regarding clinical trials for these indications, we do not know if the FDA will propose additional changes to our proposed Phase 3 clinical trial design;
- potential difficulties in defining the indication for BBS, (or any new syndromic indications we may study), as there may be discrepancies between the syndromic, or clinical definition of the syndrome, and the genetic confirmation of the indication. For example, one of our syndrome patients without genetic BBS confirmation showed little response to setmelanotide;
- potential difficulties in defining the indications for MC4R pathway heterozygous or epigenetic disorders, as well as for potential new MC4R pathway indications;

- lack of ability to predict which patients will have the most consistent responses to setmelanotide in the patients with rare genetic disorders of obesity that we are studying, as not all patients may show robust, or even any response to treatment, or may not persist in their response to treatment;
- MC4R pathway heterozygous deficiency may have additional challenges, including that the FDA, the EMA, or the equivalent competent authorities in foreign jurisdictions may require that we show that setmelanotide works better in these patients than in the genetically normal population; other challenges associated with these patients may include the need to study larger numbers of patients than for our first two indications, additional delays in initiating clinical trials for this indication due to uncertainty about the subset of these patients who will respond effectively to setmelanotide, and the lack of discussion for this indication with the FDA;
- reports from preclinical or clinical testing of other weight loss therapies may raise safety or efficacy concerns;
- patient compliance with or adherence to medication and retaining patients who have enrolled in a clinical trial but may be prone to withdraw due to rigors of the clinical trial, lack of efficacy, side-effects, personal issues or loss of interest, which might have an important impact on our primary pivotal trial endpoints for responders;
- dose responses may be different in the populations studied and may relate to a lack of a complete understanding of the absorption, distribution, metabolism and excretion of setmelanotide, or an incomplete set of clinical pharmacology studies to support labeling; 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.

The outbreak of the novel coronavirus disease, COVID-19, could adversely impact our business, including our preclinical studies, clinical trials and our commercialization prospects.

In December 2019, a novel strain of coronavirus, which causes COVID-19, was reported to have surfaced in Wuhan, China. Since then, the COVID-19 coronavirus has spread to multiple countries, including the United States, Canada and Europe, where we have planned or ongoing preclinical studies and clinical trials. On March 11, 2020, the

World Health Organization declared the outbreak of COVID-19 as a global pandemic. On March 23, 2020, the governor of Massachusetts ordered the closure of all non-essential businesses effective March 24, 2020, through May 4, 2020. Because of the nature of our operations, we are currently considered to be an essential business so, to date, our operations have only been partially affected by this order. 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 closed our principal executive office with all employees continuing their work outside of our office and restricted travel. If the COVID-19 coronavirus continues to spread in the United States and elsewhere, we may experience 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 our planned clinical trials;
- 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 coronavirus 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 the 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;
- 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 acquire COVID-19 while the clinical trial is ongoing, which could impact the results of the clinical trial, including by increasing the number of observed adverse events;
- interruptions or delays in preclinical studies due to restricted or limited operations at our research and development laboratory facility;
- delays in necessary interactions with local regulators, ethics committees and other important agencies and contractors due to limitations in employee resources or forced furlough of government employees;
- limitations in employee resources that would otherwise be focused on the conduct of our clinical trials, including because of sickness of employees or their families or the desire of employees to avoid contact with large groups of people;
- refusal of the FDA to accept data from clinical trials in affected geographies;
- impacts from prolonged remote work arrangements, such as increased cybersecurity risks and strains on our business continuity plans; and

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

The COVID-19 pandemic continues to rapidly evolve. The extent to which the pandemic impacts our business, preclinical studies, clinical trials and our commercialization prospects will depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as the ultimate geographic spread of the disease, the duration of the pandemic, travel restrictions and social distancing in the United States and other countries, business closures or business disruptions and the effectiveness of 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.

Changes in regulatory requirements, FDA or EMA guidance or unanticipated events during our clinical trials of setmelanotide may occur, which may result in changes to clinical trial protocols, changes to instruments for measuring subjective systems or additional clinical trial requirements, which could result in increased costs to us and could delay our development timeline.

Changes in regulatory requirements, FDA guidance, guidance published by the EMA or the other competent authorities in foreign jurisdictions, or unanticipated events during our clinical trials may force us to amend clinical trial protocols or the FDA, or the other competent authorities in foreign jurisdictions may impose additional clinical trial requirements. For instance, the FDA issued draft guidance on developing products for weight management in February 2007. In March 2012, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee met to discuss possible changes to how the FDA evaluates the cardiovascular safety of weight-management drugs, and the FDA may require additional studies to support registration. In addition, the FDA is considering broader applicability of requirements for cardiovascular outcomes trials, or CVOTs, presenting the possibility of cardiovascular risk pre-approval, including for obesity products. While our Phase 3 discussions with the FDA have not resulted in a requirement for any of these activities, any future requirement for these activities could result in additional clinical requirements for setmelanotide, increase our costs and delay approval of setmelanotide.

Amendments to our clinical trial protocols would require resubmission to the FDA and IRBs or other competent authorities and ethics committees in foreign jurisdictions for review and approval, which may adversely impact the cost, timing or successful completion of a clinical trial. If we experience delays completing, or if we terminate, any of our clinical trials, or if we are required to conduct additional clinical trials, the commercial prospects for setmelanotide may be harmed and our ability to generate product revenue will be delayed.

In addition, as part of commencing our Phase 3 clinical trial for setmelanotide in POMC deficiency obesity, we sought FDA concurrence with, and received substantial input on, the use of Patient Reported Outcome, or PRO, and Observer Reported Outcome, or ORO, questionnaires for measuring subjective endpoints for changes in hunger and/or food-seeking behavior and compulsions. We applied the same guidance in our Phase 3 clinical trial for setmelanotide in LEPR deficiency obesity and believe we can apply the same guidance to our future pivotal trials in other indications. A PRO is a measurement based on a report that comes from the patient about the status of a patient's health condition, without amendment or interpretation of the patient's response by a clinician or anyone else. An ORO is a measurement based on an observation by someone other than the patient or a health professional, such as a parent, spouse or other non-clinical caregiver who is in a position to regularly observe and report on a specific aspect of the patient's health. In our Phase 3 clinical trials for setmelanotide, based on the FDA feedback, we plan to measure the ability of setmelanotide to mitigate hunger and/or hyperphagia, the overriding physiological drive to eat, through PRO and ORO questionnaires. The questionnaires are designed to elicit feedback from patients on how well setmelanotide decreases their hunger, and from their family members or caregivers on the effect of setmelanotide on the patients' food seeking behavior.

To our knowledge, no sponsor of an approved drug has yet used PRO or ORO questionnaires to generate data on hyperphagia or hunger mitigating endpoints. Because we may be relying on clinical endpoints that have not previously been the subject of prior FDA approvals, there is a risk that the FDA or other equivalent competent authorities in foreign jurisdictions may not consider the endpoints to provide evidence of clinically meaningful results or that results may be

difficult for the FDA or other equivalent competent authorities in foreign jurisdictions to interpret, in particular for the pediatric age group. If we experience delays in our ongoing validation of our PRO or ORO questionnaires, or do not receive agreement with those proposed questionnaires based on the conceptual framework, content reliability, other measures of validity, or their ability to detect changes in hyperphagia or hunger, or we experience difficulties in the methods of statistical analysis for hunger and hyperphagia, we may experience delays in our trials or in product approval as well as be unable to reference data on hyperphagia or hunger in our product labeling, if any. Finally, our Phase 3 clinical trials assess hunger using multiple methods, some of which were previously used in Phase 2, but some of which were initiated in Phase 3 trials and for which little data is available. Hence it is possible that the effects on hunger seen in Phase 2 trials may differ with some of the methodologies for assessing hunger being used in Phase 3 trials, or may not support language in the proposed product labeling.

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

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 regulatory approval by the FDA or other equivalent competent authorities in foreign jurisdictions.

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.

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.

The safety data we have disclosed to date represents our interpretation of the data at the time of disclosure and they are subject to our further review and analysis. There has been only a single serious adverse event, or SAE, reported in a patient taking setmelanotide and attributed as possibly related to treatment in our clinical trials. In our Phase 2 clinical trial with once daily SC injection, one patient was hospitalized for unusual chest pain, but no evidence of any serious respiratory or cardiac cause was found after careful evaluation and the event was attributed to musculoskeletal pain. There

were no treatment related changes in physical examination, except as noted below, and few, if any, clinically relevant changes in electrocardiograms, laboratory data and/or anti-drug antibodies. In addition to the SAE described above, there have been a moderate number of additional incidents overall which have led to SAEs in the full development program, which have been determined not to be related to setmelanotide treatment. These have included patients on setmelanotide, as well as patients who were not taking setmelanotide. There has been no pattern to these unrelated serious adverse experiences. There has also been a SAE with respect to a study participant on setmelanotide in our Phase 3 pivotal study for LEPR deficiency obesity who died in a fatal motor vehicle accident, in which the driver lost control, and our study participant was a passenger. This was determined not to be related to setmelanotide treatment. In addition, one study participant withdrew from our Phase 3 pivotal study for LEPR deficiency obesity before the end of the titration due to mild hypereosinophilia, which was determined not to be related to setmelanotide treatment.

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.

In addition, our interpretation of the safety data from our clinical trials is contingent upon the review and ultimate approval of the FDA, other regulatory authorities or other equivalent competent authorities in foreign jurisdictions. The FDA or other equivalent competent authorities in foreign jurisdictions may not agree with our methods of analysis or our interpretation of the results. In addition, the long-term effects of setmelanotide have only been tested in a limited number of patients.

Further, if setmelanotide receives marketing approval and we or others identify undesirable side effects caused by the product, or any other similar product, before or after the approval, 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. Even under these circumstances, we may not be granted pediatric approval from the FDA for these indications. 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, or PREA.

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. For example, if the FDA were to refuse to recognize all MC4R pathway deficiencies as separate diseases or conditions, the population of patients in the United States with a particular disease or condition, as defined by the FDA, who would be appropriate candidates for setmelanotide could be more than 200,000 or more individuals. In that event, the drug may not qualify for orphan drug designation by the FDA, even if the population of patients with a specific MC4R pathway deficiency for which we seek approval is lower than 200,000. Additionally, the designation of setmelanotide as an orphan drug does not guarantee that the FDA will accelerate regulatory review of, or ultimately approve, setmelanotide.

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.

The FDA Reauthorization Act of 2017 amended the FDCA by codifying the FDA's pre-existing regulatory interpretation, to require that a drug sponsor demonstrate the clinical superiority of an orphan drug that is otherwise the same as a previously approved drug for the same rare disease in order to receive orphan drug exclusivity. The new law reversed prior precedent holding that the Orphan Drug Act unambiguously requires that the FDA recognize the orphan exclusivity period regardless of a showing of clinical superiority. The FDA may further reevaluate the Orphan Drug Act and its regulations and policies. We do not know if, when, or how the FDA may change the orphan drug regulations and policies in the future, and it is uncertain how any changes might affect our business. Depending on what changes the FDA may make to its orphan drug regulations and policies, our business could be adversely impacted.

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

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

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

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

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

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

We have entered into a license agreement with Camurus AB, or Camurus, for the use of Camurus' drug delivery technology, FluidCrystal, to formulate once-weekly setmelanotide. This formulation, if successfully developed for setmelanotide, will be delivered subcutaneously, similar to our once-daily formulation, except that we anticipate it will be injected once weekly. The initial Phase 1 pharmacokinetic data from healthy obese volunteers supports once-weekly dosing, but has only been administered for short durations, with longer studies in process. It is possible that the tolerability profile and/or pharmacokinetics in patients will not be similar to that of healthy obese volunteers, making development of this product more complex. In addition, while we have started consultations with regulatory authorities about the 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. A medicinal product called Buxidol in the EU and Brixadi in the United States (buprenorphine,) that contains the Camurus formulation has been authorized to be marketed in the EU by the European Commission to treat dependence on opioids. In December 2018, Brixadi was granted tentative approval for treatment of Opioid Use Disorder, or OUD, in the United States, subject to expiration of an exclusivity period granted to another product, Sublocade, which is based upon a different formulation of buprenorphine. Excluding this, Camurus formulations have not been approved for any product by the FDA at this time, which further complicates our understanding for the path to approval.

We are seeking FDA approval of the once-daily formulation in the initial NDA submission for POMC deficiency obesity and LEPR deficiency obesity, and 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-daily formulation and/or 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 approval or CE mark of an in vitro companion diagnostic device to ensure appropriate selection of patients as a condition of approving setmelanotide. The development and approval or CE mark of an in vitro companion diagnostic device would require substantial financial resources and could delay regulatory approval of setmelanotide.

We have focused our development of setmelanotide as a treatment for obesity caused by certain genetic deficiencies affecting the MC4R pathway. In order to assist in identifying this subset of patients, we employ a genetic diagnostic test, which is a test or measurement that evaluates the presence of genetic variants in a patient. The FDA has previously advised that for our clinical trial of setmelanotide to treat POMC deficiency obesity, it will be sufficient to use

genetic diagnostic testing known as Sanger bi-directional nucleotide sequencing, as long as that testing is performed by laboratories meeting the standards of the Clinical Laboratory Improvement Amendments, or CLIA, for Laboratory Developed Tests, or LDTs. Currently the Centers for Medicare and Medicaid Services, or CMS, regulates LDTs and the laboratories that develop them, and enforces CLIA. CMS evaluates whether there is clinical utility for each specific test, and also performs post-market oversight of laboratory operational processes. CMS coverage determinations of clinical utility measure the ability of the test to impact clinically meaningful health outcomes, such as mortality or morbidity, through the adoption of efficacious treatments. CMS' oversight through the CLIA program is designed to confirm that a lab assesses analytical validity, but does not confirm whether it had results from an analytical validity assessment that were sufficient to support the claimed intended use of the test. The FDA has issued guidance and has provided comments to members of Congress indicating, however, that in the future it intends to assert jurisdiction over LDTs and to increase regulatory requirements for LDTs. If the FDA does so, the burdens and costs of using LDTs to select patients for setmelanotide could increase, the availability of those LDTs could be negatively affected, and our development program for setmelanotide could be delayed, which in turn could delay or impair our ability to proceed to commercialization.

The FDA recently reiterated its position that an LDT is sufficient for identifying patients in our clinical trials, but the agency also recently indicated that approval of an *in vitro* companion diagnostic device will be needed. *In vitro* companion diagnostic devices, or companion diagnostics, provide information that is essential for the safe and effective use of a corresponding therapeutic product. These companion diagnostics may be co-developed with a device manufacturer or with a laboratory, and generally require FDA approval as well. The FDA stated that absence of complete development of a companion diagnostic would not preclude us from submitting an NDA or preclude the FDA from reviewing it. The FDA also stated that completing development of a companion diagnostic as a post-marketing commitment or a post-marketing requirement is a possibility, assuming that upon review, no issues related to efficacy or safety arise that would necessitate a companion diagnostic at the time of approval. The FDA has indicated it will work with us to identify the least burdensome analytical validation approach to a companion diagnostic for setmelanotide. We are engaged in ongoing discussions with the FDA regarding development of a Class II companion diagnostic.

We may face significant delays or obstacles in obtaining approval of an NDA, or of comparable foreign marketing authorization for setmelanotide as the FDA or other equivalent competent authorities in foreign jurisdictions may take the position that a companion diagnostic device is required prior to granting approval of setmelanotide. In addition, we are dependent on the sustained cooperation and effort of third-party collaborators with whom we partner with to develop companion diagnostics. We and our current and future collaborators may encounter difficulties in developing such tests, including issues relating to the selectivity and/or specificity of the diagnostic, analytical validation, reproducibility or clinical validation. 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 approval of setmelanotide.

If the FDA deems setmelanotide to require a companion diagnostic to accurately identify the patients who belong to the target subset, the FDA may require product labeling that limits use to only those patients who express the genetic variants identified by the device. Moreover, even if setmelanotide and a companion diagnostic are approved together, the device itself may be subject to reimbursement limitations that could limit access to treatment and therefore adversely affect our business and financial results.

We also are discussing with the FDA the specific mutations, or variants, that will define each indication for which we intend to seek approval. Our efforts have focused on loss-of-function variants that effectively inactivate the genes in the MC4R pathway, and we and the FDA have agreed on a path to define these variants for approval, which can also be used to categorize new variants as they are identified and that has been used for other diagnostics. These approaches are complex, and the impact on the size of the indicated patients is not certain.

In addition, we intend to continue to apply genetic tests to address goals beyond seeking FDA approval of setmelanotide, including supporting efforts to explore and expand the diagnosis of patients with genetic causes of obesity, and to assist in building awareness of these illnesses. As such, we may develop or work with partners to develop additional genetic tests in the area of genetic obesity, including panels that may study a larger number of genes. There are many factors that might influence the success of these efforts, which could be impactful on our commercial efforts, including the cost, analytical methods, and the ability to provide clinical and diagnostic information to patients and doctors. In

addition, the process of conversion of patients with a genetic diagnosis of MC4R pathway disorders to patients receiving treatment is still uncertain and may be complex.

We have only one product candidate in clinical development and we may not be successful in any future efforts to identify and develop additional product candidates.

We have only one product candidate in clinical development and may seek to identify and develop additional product candidates for clinical development, both within and outside of our current area of expertise. If so, the success of our business may depend primarily on our ability to identify, develop and commercialize these products. Research programs to identify new product candidates require substantial technical, financial and human resources. We may fail to identify other potential product candidates for clinical development for a number of reasons. Our research methodology may be unsuccessful in identifying potential product candidates or our potential product candidates may be shown to have harmful side effects or may have other characteristics that may make the products unmarketable or unlikely to receive marketing approval. We may focus our efforts and resources on potential programs or product candidates that ultimately prove to be unsuccessful. In addition, any such efforts could adversely impact our continued development and commercialization of setmelanotide.

If any of these events occur, we may be forced to abandon some or all of our development efforts for a program or programs, which would have a material adverse effect on our business and could potentially cause us to cease operations.

Prader-Willi syndrome, or PWS, is a complex disease, and companies have had difficulties in developing new therapies for PWS.

Although we have been granted orphan drug designation in the United States and the EU for setmelanotide in treating PWS, we are not moving directly towards a Phase 3 trial in PWS at this time, but instead will be continuing to evaluate setmelanotide in another Phase 2 trial. We do not know the probability that we will be able to succeed in this additional Phase 2 trial and/or to proceed to Phase 3 and/or approval, even when these efforts are completed. In addition, the experience by others suggests that PWS patients are at risk for adverse experiences and for this, and many other reasons, clinical trials in that population are challenging. It may be both difficult to determine if adverse effects in this population are due to the disease, setmelanotide or some combination of both. PWS is a complex multigenic disease, and the hypothesis that PWS is an upstream MC4R pathway disorder is supported primarily on the role of genes, such as MAGEL2 and PCSK1 (also known as PC1), in animal models of obesity. Our results may support that PWS is not an upstream MC4R pathway disorder. Alternatively, other design factors may have influenced the outcome of this trial, and we will be reassessing the possibility of future Phase 2 trials in PWS that address the following potential factors: duration of treatment, younger age of population, improved setmelanotide pharmacokinetics, consideration of higher doses, and operational limitations of the completed Phase 2 trial. There can be no assurances that some of the factors that affected the results of the PWS trials will not also adversely impact the results of our trials for other indications.

In addition, we have begun a program for a new mechanism that may have therapeutic effects in PWS, but this program is in preclinical development, and our candidate, RM-853, may not succeed in completing the pre-IND studies needed to proceed to clinical trials, or may fail in early Phase 1 studies due to unfavorable safety, pharmacokinetics or for other reasons. The hypothesis supporting the therapeutic effects of this mechanism is also based on limited clinical and preclinical information, and even if RM-853 were to progress to a Phase 2 proof of concept study, it is unclear if there will be safety and efficacy to support proceeding further in development.

Risks Related to the Commercialization of Setmelanotide

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.

Our ability to commercialize setmelanotide 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.

Third-party payors increasingly are challenging prices charged for pharmaceutical products and services. 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.

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.

Moreover, 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. We may experience pricing pressures in connection with the sale of setmelanotide or our product candidates due to the trend toward managed health care, the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and biologics and surgical procedures and other treatments, has become intense. As a result, increasingly high barriers are being erected to the entry of new products.

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

In the EU, in particular, each EU member state can restrict the range of medicinal products for which its national health insurance system provides reimbursement and can control the prices of medicinal products for human use marketed in its territory. As a result, following receipt of marketing authorization in an EU member state, through any application route, an applicant is required to engage in pricing discussions and negotiations with the competent pricing authority in the individual EU member states. Some EU member states operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed upon. Other EU member states approve a specific price for the medicinal product or may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. The downward pressure on healthcare costs in general, particularly

prescription drugs, has become more intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, we may face competition for setmelanotide from lower priced products in foreign countries that have placed price controls on pharmaceutical products.

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

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

We do not currently have infrastructure in place for the sale, marketing or distribution of pharmaceutical products. In order to market setmelanotide, if approved by the FDA or other equivalent competent authorities in foreign jurisdictions, we must build our sales, marketing, managerial and other non-technical capabilities or make arrangements with third parties to perform these services. 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.

Even if we receive marketing approval for setmelanotide in the United States, we may never receive regulatory approval to market setmelanotide outside of the United States.

We intend to seek marketing authorization for setmelanotide in the EU and in other countries worldwide. In order to market any product outside of the United States, we must establish and comply with the numerous and varying safety, efficacy and other regulatory requirements of other countries. Marketing authorization procedures vary among countries and can involve additional setmelanotide testing and additional administrative review periods. The time required to obtain marketing authorization in other countries might differ from that required to obtain FDA approval. The marketing authorization processes in other countries may implicate all of the risks detailed above regarding FDA approval in the United States as well as other risks. In particular, in many countries outside of the United States, products must receive pricing and reimbursement approval before the product can be commercialized. Obtaining this approval can result in

substantial delays in bringing products to market in such countries. Grant of marketing authorization in one country does not ensure grant of marketing authorization in another country, but a failure or delay in obtaining marketing authorization in one country may have a negative effect on the regulatory process or commercial activities in others. Failure to obtain marketing authorization in other countries or any delay or other setback in obtaining such authorizations would impair our ability to market setmelanotide in such foreign markets. Any such impairment would reduce the size of our potential market share and could have a material adverse impact on our business, results of operations and prospects.

Even if we receive marketing approval for setmelanotide, we may not achieve market acceptance, which would limit the revenue that we generate from the sale of setmelanotide.

The commercial success of setmelanotide, if approved by the FDA or other equivalent competent authorities in foreign jurisdictions, will also depend upon the awareness and acceptance of setmelanotide within the medical community, including physicians, patients and third-party payors. If setmelanotide is approved but 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, setmelanotide also provides incremental health benefits to patients. Our efforts to educate the medical community and third-party payors about the benefits of setmelanotide may require significant resources and may never be successful. All of these challenges may impact our ability to ever successfully market and sell setmelanotide.

Market acceptance of setmelanotide, if approved, will depend on a number of factors, including, among others:

- the ability of setmelanotide to treat 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 setmelanotide;
- the relative convenience and ease of SC injections as the necessary method of administration of setmelanotide, including as compared with other treatments for obese patients;
- the prevalence and severity of any adverse side effects associated with setmelanotide;
- limitations or warnings contained in the labeling approved, as well as the existence of a REMS, for setmelanotide 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 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 setmelanotide to treat the maximum range of pediatric patients, and any limitations on its indications for use, such as if the labeling limits the approved population to patients ages 12 and above;
- the strength of marketing and distribution support and timing of market introduction of competitive products;

- publicity concerning setmelanotide or competing products and treatments;
- pricing and cost effectiveness;
- the effectiveness of our sales and marketing strategies;
- our ability to increase awareness of setmelanotide 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 the FDA or other equivalent 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 setmelanotide, 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 setmelanotide obsolete or uneconomical. Any new product that competes with an approved product may need to demonstrate compelling advantages in efficacy, convenience, tolerability and safety to be commercially successful. Other competitive factors, including generic competition, could force us to lower prices or could result in reduced sales. In addition, new products developed by others could emerge as competitors to setmelanotide. If we are not able to compete effectively against our current and future competitors, our business will not grow and our financial condition and operations will suffer.

Currently, there are no approved or effective treatments for regulating hunger and hyperphagia related behaviors of patients with POMC deficiency obesity, LEPR deficiency obesity, BBS, Alström syndrome, POMC heterozygous deficiency obesity, POMC epigenetic disorders, SRC1 deficiency obesity, SH2B1 deficiency obesity, MC4R deficiency obesity, or Smith-Magenis syndrome. Bariatric surgery is not a treatment option for these genetic disorders of obesity because the severe obesity and hyperphagia associated with these disorders are considered to be risk factors for bariatric surgery. While we are unaware of any competitive products in clinical development for the obesity and hyperphagia caused by upstream MC4R pathway deficiencies specifically, 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 setmelanotide, if approved, 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 setmelanotide. 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 setmelanotide 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 setmelanotide 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. If and when we obtain marketing approval for setmelanotide, we intend 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.

Risks Related to Our Dependence on Third Parties

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 regulatory approval 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 Good Clinical Practices, or cGCPs, 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.

We rely completely on third-party suppliers to manufacture our clinical drug supplies of setmelanotide, and we intend to rely on third parties to produce commercial supplies of setmelanotide and 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 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 would be conducted after we submit 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. If we import any drugs or drug substances, we would be subject to FDA 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 various third parties for the manufacture of setmelanotide and intend to continue to do so in the future. We have entered into process development and manufacturing service agreements with three CMOs: Corden Pharma Brussels S.A, or Corden, (formerly Peptisyntha SA prior to its acquisition by Corden), PolyPeptide Group, Baine L'Alleud, or PPL, and Neuland Laboratories, in connection with certain process development and manufacturing services for regulatory starting materials and/or drug substance, or API in connection with the manufacture of setmelanotide. We have also entered into a process development and manufacturing services agreement with Recipharm Monts S.A.S, or Recipharm, under which Recipharm will provide certain process development and manufacturing services in connection with the manufacture of setmelanotide drug product. 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. The agreement with Corden also provides that, subject to certain conditions, for a period following each product launch date, we will source from Corden a portion of our requirements for that product being sourced from non-affiliate third parties. We may need to engage additional third-party suppliers to manufacture our clinical drug supplies. In the future, if we approach commercialization of setmelanotide or any future product candidate, we will need to engage other third parties to assist in, among other things, labeling, packaging, distribution, post-approval safety reporting and pharmacovigilance activities. We cannot be certain that we can engage third-party suppliers on terms as favorable as those that are currently in place.

We do not perform the manufacturing of any drug products and are completely dependent on our CMOs to comply with cGMPs for manufacture of both API and finished drug product. We recognize that we are ultimately responsible for ensuring that our drug substances and finished 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 currently in the process of manufacturing finished drug product for use in our upcoming clinical trials. We believe we currently have a sufficient amount of finished setmelanotide, diluent and placebo to complete our planned clinical trials. 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, 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 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 both the preclinical and clinical trials. Additionally, as our CMOs are producers of drug substances and drug products, including vaccines and therapeutics, they could be compelled by a national government, or choose themselves, to shift their resources to the production of a COVID-19 vaccine and/or therapeutics for COVID-19, which could disrupt any scheduled drug substance or drug product batches we may have and may prevent us from obtaining supplies for our programs in a timely manner to meet our development timelines.

We do not have long-term supply agreements in place with our contractors, and each batch of setmelanotide is individually contracted under a quality and supply agreement. 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, if approved. Our current scale of manufacturing appears adequate to support all of our current needs for clinical trial supplies for setmelanotide. If setmelanotide is approved, we will need to identify 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 district 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 setmelanotide, if approved, 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 setmelanotide, if approved.

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. For example, we received a letter in January 2013 from a third party bringing to our attention several patents and patent applications, both U.S. and non-U.S. We responded in April 2013 and have not received any further correspondence since then. All but a few of the patents and patent applications mentioned in the letter were abandoned or not in force at the time the letter was sent to us. Although subsequent to our response, the third party has allowed all the remaining patents to lapse for non-payment of patent maintenance fees, we cannot assure you that the holder of these third-party patents will not attempt to assert these patents against us.

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 setmelanotide.

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.

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.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

The U.S. Patent and Trademark Office, or U.S. PTO, and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other provisions during the patent process. There are situations in which noncompliance can result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, competitors might be able to enter the market earlier than would otherwise have been the case.

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, if approved.

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 have licensed our rights to RM-853 from Takeda Pharmaceutical Company Limited, or Takeda. Our license with Takeda imposes various obligations on us, and provides Takeda the right to terminate the license in the event of our material breach of the license agreement, if we voluntarily or involuntarily file for bankruptcy, or for our bringing an action seeking to have a Takeda license patent right declared invalid. Termination of our license from Takeda would result in our inability to use the licensed intellectual property.

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

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, if approved, as well as harm our competitive business position and our business prospects.

We have not yet registered trademarks for a commercial trade name for setmelanotide and failure to secure such registrations could adversely affect our business.

We have not yet registered trademarks for a commercial trade name for setmelanotide. Any future 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. Moreover, any name we propose to use for setmelanotide in the United States must be approved by the FDA, regardless of whether we have registered it, or applied to register it, as a trademark. The FDA typically conducts a review of proposed product names, including an evaluation of potential for confusion with other product names. If the FDA objects to any of our proposed product names, we may be required to expend significant additional resources in an effort to identify a suitable substitute name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA.

Similar rules apply in the EU. Any brand name we propose for setmelanotide in the EU 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 names, 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. 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.

While we believe that setmelanotide contains active ingredients that would be treated by the FDA as a new chemical entity, or a new drug product, and, therefore, if approved, should be afforded five years of marketing exclusivity, the FDA may disagree with that conclusion and may approve generic products within a period that is less than five years. 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 approvals for the commercialization of setmelanotide. We depend entirely on the success of setmelanotide, which is in Phase 3 clinical development for treatment of POMC deficiency obesity, LEPR deficiency obesity, Bardet-Biedl syndrome and Alström syndrome. We cannot be certain that we will be able to obtain regulatory approval for, or successfully commercialize, setmelanotide. If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we will not be able to commercialize setmelanotide, 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. We currently have no drug products for sale and may never be able to develop marketable drug products. Setmelanotide, which is currently in Phase 3 clinical development as a treatment for genetic deficiencies affecting the MC4R pathway, including POMC deficiency obesity, LEPR deficiency obesity, BBS and Alström syndrome, will require substantial additional clinical development, testing and regulatory approval before we are permitted to commence commercialization. The clinical trials of setmelanotide are, and the manufacturing and marketing of setmelanotide will be, 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. When a sponsor relies exclusively or predominantly on foreign clinical data, the FDA may require a showing that those data are applicable to the U.S. population and U.S. medical practice, which in some cases may require bridging studies or other evidence. Of the large number of drugs in development in the United States and in other countries, only a small percentage will

successfully complete the FDA regulatory approval process or the equivalent process in foreign jurisdictions and will be commercialized. In addition, we have not discussed all of our proposed development programs with the FDA or the competent authorities of foreign jurisdictions. Accordingly, even if we are able to obtain the requisite financing to continue to fund our development and clinical trials, we cannot assure you that setmelanotide will be successfully developed or commercialized.

We are not permitted to market setmelanotide in the United States until we receive approval of an NDA from the FDA, or in any foreign jurisdictions until we receive the requisite approval from the competent authorities in such countries. We have three Phase 3 clinical trials underway, one each for the treatment of POMC deficiency obesity and LEPR deficiency obesity, and a third combined Phase 3 trial for BBS and Alström syndrome. We recently reported topline data in our Phase 3 clinical trials for the treatment of POMC deficiency obesity and LEPR deficiency obesity and based on these results, we submitted an NDA to the FDA on March 27, 2020. Under our current development program, we are conducting a single Phase 3 clinical trial for POMC deficiency obesity. To date, in our ongoing discussions with the FDA, the FDA has not asked for additional Phase 3 trials in POMC deficiency obesity, but the FDA could still require us to conduct additional Phase 3 clinical trials for this indication. Moreover, for POMC deficiency obesity, the FDA has provided clear advice in the past, but could at any time alter its previous advice on many aspects of the trial—the small size, the primary and key secondary endpoints, the open label design, the amount of past medical history available on individual patients, the statistical analysis plan, the definition of clinically-relevant success for the protocol, entry of patients ages six or over—all of which may impact the timing and ability to obtain FDA approval. For example, the FDA asked us in December 2017 to switch the order of our primary and key secondary endpoints for weight in our POMC deficiency Phase 3 protocol. While this might be favorable as the new primary endpoint has increased statistical power—the ability to produce a positive study result—this change occurred after the Phase 3 trial had started and may result in additional complexities such as more attention to compliance and retention. There are other aspects of the trial for which we have not received advice from the FDA, such as the number of U.S. versus non-U.S. patients and the number of patients with POMC gene defects versus the number of patients with PCSK1 defects, which could also impact the timing of and our ability to obtain FDA approval. We have also received FDA comments that indicate the Phase 3 program for LEPR deficiency obesity can be similar to POMC deficiency obesity and are conducting our Phase 3 trial for LEPR deficiency obesity in a similar way based in part on those comments. Similarly, the preliminary FDA advice on the design of the BBS and Alström syndrome combined clinical Phase 3 study could, at any time, be altered by the FDA, including for example, the size of the trial, the type and importance of endpoints, the length of the trial, the ability to combine the two indications, the inclusion of pediatric patients and pediatric efficacy endpoints, the design for any placebo-controlled aspect of the trial, as well as other factors that could impact on the ability of the trial to support registration.

In addition, the FDA and other equivalent competent authorities in foreign jurisdictions will expect for there to be little, or no introduction of bias in the open-label Phase 3 trials. Accordingly, we have agreed with the FDA, and implemented in our pivotal studies, that little, if any, efficacy data will be available to us in any form until the Phase 3 trials are complete.

The FDA or other regulatory authorities and other equivalent competent authorities in foreign jurisdictions will also require that we conduct one or more pivotal trials for each other indication sought. In addition, we are not sure if one or more Phase 3 trials would be required for approval in each other indications. The need and length of placebo-controlled data in these pivotal trials and the number of patients required for these approvals is also unclear.

We will determine in our own judgment if a non-pivotal trial meets “proof of concept” in each of these indications. There is no certainty that the FDA, other competent authorities, or outside investors will agree with our determination, which might have an impact on the ability to transition to Phase 3 studies.

In the EU we are currently conducting the Phase 3 clinical trial RM-493-012 in Germany, France, Belgium, Spain and the United Kingdom for POMC deficiency obesity. We are also conducting this trial in the United States and Canada. On March 23, 2017, we received EMA scientific advice on the appropriateness and sufficiency of the non-clinical and clinical development programs to support an initial marketing authorization application in POMC deficiency obesity. The EMA scientific advice included preliminary advice on the clinical trial RM-493-012. The EMA expressed general support for the ongoing Phase 3 program in POMC deficiency obesity. The EMA advised that the regulatory strategy for a rare disorder is supported and that the EMA may have to rely on scarce data. The EMA also advised, however, that we need to

consider whether full approval or approval under conditional or exceptional circumstances would be the most appropriate pathway for application for POMC deficiency obesity.

In 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 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 us with guidance concerning the development of setmelanotide. The PRIME designation does not, however, guarantee that the regulatory review process in the EU will be shorter or less demanding. Neither does the PRIME designation guarantee that the European Commission will grant a marketing authorization for setmelanotide.

In the EU we are currently conducting the Phase 3 clinical trial RM-493-015 in Germany, France, Netherlands, and the United Kingdom, for LEPR deficiency obesity. We are also conducting this trial in the United States. We have not obtained EMA scientific advice for the LEPR deficiency obesity indication, nor have we obtained EMA scientific advice for the BBS or Alström syndrome indications, except in the more general setting of our PRIME discussions.

Given the orphan status of setmelanotide for the treatment of POMC deficiency obesity in the EU the application for marketing authorization for a POMC deficiency obesity indication must be submitted via the centralized procedure. In November 2018, we obtained orphan designation in the EU for setmelanotide for the treatment of LEPR deficiency obesity. In addition, we have submitted a PIP for setmelanotide to the EMA Pediatric Committee, or PDCO, in 2017. By a decision in June 2018, the EMA formally accepted the PIPs for setmelanotide in the treatment of appetite and general nutritional disorders, including the deferral and the waiver requested by us.

We cannot assure you that the clinical trials we are conducting in the EU will be completed in a timely manner. Similar to the United States, we are subject to comprehensive regulatory oversight by the competent authorities of the individual EU member states where we are conducting our clinical trials. Failure by us or by any of our third party partners to comply with EU laws and the related national laws of individual EU member states governing the conduct of clinical trials may result in the suspension of clinical trials or in other administrative, civil or criminal penalties.

Our plan is to expand our internal clinical development operations and capabilities so that we can continue to manage our Phase 3 clinical trials. We believe we have finalized the design, timing and size of our Phase 3 trial for POMC deficiency obesity with the FDA but we cannot assure you that the trial will not be subject to further modification.

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

- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may disagree with our interpretation of data from clinical trials, or may change the requirements for approval even after it has reviewed and commented on the design for our clinical trials;
- we may not be able to demonstrate to the satisfaction of the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions that setmelanotide is safe and effective in treating obesity caused by certain genetic deficiencies affecting the MC4R pathway;
- the results of our clinical trials may not be interpretable or meet the level of statistical or clinical significance required by the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions for marketing approval. For example, the potential unblinding of setmelanotide studies due to easily identifiable AEs may raise the concern that potential bias has affected the clinical trial results;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may disagree with the number, size, conduct or implementation of our clinical trials;

- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may require that we conduct additional clinical trials or pre-clinical studies;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may not consider that our diagnostic strategy supports approval;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may decide that additional assays or data to understand any risks for anti-drug antibodies may need to be available for approval;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may decide that the toxicology program, including any parts of carcinogenicity studies that are filed, do not meet the requirements for approval;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions or the applicable foreign regulatory agency may identify deficiencies in our chemistry, manufacturing or controls of setmelanotide, or in the commercial production of setmelanotide to support product approval;
- the CROs that we retain to conduct our clinical trials may take actions outside of our control that materially adversely impact our clinical trials;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may find the data from preclinical studies and clinical trials insufficient to demonstrate that clinical and other benefits of setmelanotide outweigh its safety risks;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may disagree with our interpretation of data from our preclinical studies and clinical trials;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may not approve the formulation, labeling or specifications of setmelanotide;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may not accept data generated at our clinical trial sites;
- if and when our NDA or our MAA is submitted and reviewed by an advisory committee, the FDA, the EMA, or the equivalent competent authorities in foreign jurisdictions may have difficulties scheduling an advisory committee meeting in a timely manner or the advisory committee may recommend against approval of our application or may recommend that 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;
- if any NDA is approved, we may be required to conduct additional studies and clinical trials or other post-market requirements to assess possible serious risks;
- the FDA may require development of a REMS as a condition of approval or post-approval, or may not agree with our proposed REMS or may impose additional requirements that limit the promotion, advertising, distribution, or sales of setmelanotide. In addition, 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 regulatory approval for and successfully market setmelanotide. Moreover, because our business is entirely dependent upon setmelanotide, any such setback in our pursuit of regulatory approval 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 announced its intention to temporarily postpone routine surveillance inspections of domestic manufacturing facilities. 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 approval we are 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 U.K. Medicines and Healthcare products Regulatory Agency, including delays in granting clinical trial authorization or marketing authorization, disruption of importation and export of active substance and other components of new drug formulations, and disruption of the supply chain for clinical trial product and final authorized formulations. The cumulative effects of the disruption to the regulatory framework may add considerably to the development lead time to marketing authorization and commercialization of setmelanotide in the EU and/or the United Kingdom. Any delay in obtaining, or an inability to obtain, any marketing authorization, as a result of Brexit or otherwise, would prevent us from commercializing setmelanotide in the United Kingdom and/or the EU and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek marketing authorization in the United Kingdom and/or EU for setmelanotide, which could significantly and materially harm our business.

Even if we obtain marketing approval for setmelanotide, the terms of approval 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.

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

In addition, a sponsor's responsibilities and obligations under the FDCA and FDA regulations, and those of equivalent foreign regulatory agencies, may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any regulatory approval that we may have obtained and we may not achieve or sustain profitability, which would materially and adversely affect our business, financial condition, results of operations and prospects.

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 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.

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, prevent or delay marketing approval of setmelanotide, restrict or regulate post-approval activities and affect our ability, or the ability of any future collaborators, to profitably sell any products for which we, or they, obtain marketing approval. 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 any approved products.

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

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs, although this fee does not apply to sales of certain products approved exclusively for orphan indications;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- expansion of manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs, revising the "average manufacturer price" definition, and extending rebate liability from fee-for-service Medicaid utilization to include the utilization of Medicaid managed care organizations as well as Medicaid managed care;
- expansion of the list of entity types eligible for participation in the Public Health Service 340B drug pricing program, or the 340B program, to include certain free-standing cancer hospitals, critical access hospitals, rural referral centers, and sole community hospitals, but exempting "orphan drugs" from the 340B ceiling price requirements for these covered entities;
- establishment of the Medicare Part D coverage gap discount program requiring manufacturers to provide a then 50% (and, effective January 1, 2019, 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, potentially including prescription drug spending.

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

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

Additional changes that may affect our business include the expansion of new programs such as Medicare payment for performance initiatives for physicians under the Medicare Access and CHIP Reauthorization Act of 2015, or MACRA, which was fully implemented in 2019. At this time, it is unclear how the introduction of this Medicare quality payment program will impact overall physician reimbursement. The cost of prescription pharmaceuticals in the United States has also been the subject of considerable discussion in the United States, and members of Congress and the Administration have stated that they will address such costs through new legislative and administrative measures. There have been several Congressional inquiries and proposed bills and regulatory initiatives 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. Any specific reforms that may be enacted or implemented remain uncertain, both as to their substance and timing, and may affect a broad range of public policy considerations, including the Medicare and Medicaid programs and the FDA regulatory regime.

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 on Form 10-Q.

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 expect to participate in and have certain price reporting obligations to the Medicaid Drug Rebate Program. Under the Medicaid Drug Rebate Program, if we successfully commercialize setmelanotide, we would be required to pay a rebate to each state Medicaid program for our covered outpatient drugs that are dispensed to Medicaid beneficiaries and paid for by a state Medicaid program as a condition of having federal funds being made available to the states for our drugs under Medicaid and Medicare Part B. Those rebates are based on pricing data we would have to report 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 if we participate in the program could negatively impact our financial results.

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

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

HRSA issued a final regulation regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities, which became effective on January 1, 2019. It is currently unclear 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. If we participate in the Medicaid Drug Rebate Program and consequently the 340B program, we cannot assure you that our submissions will not be found to be incomplete or incorrect.

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

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

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

If we obtain marketing approval for setmelanotide, we will be subject to strict enforcement of post-marketing requirements and we could be subject to substantial penalties, including withdrawal of our product from the market, if we fail to comply with all regulatory requirements.

If we obtain marketing approval for setmelanotide, we will be subject to continual requirements of and review by the FDA and equivalent competent authorities in foreign jurisdictions. These requirements may include, but are not limited to, post-approval studies to be conducted which may include carcinogenicity studies, a QT interval prolongation study in one form or another, other Phase 1 trials, and ongoing natural history studies with patient registries. Other requirements may also include, among other things, restrictions governing promotion of an approved product, submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP requirements relating to

manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, and requirements regarding the distribution of samples to physicians and recordkeeping. The FDA and other federal and state agencies, including the Department of Justice and other equivalent competent authorities in foreign jurisdictions, closely regulate compliance with all requirements governing prescription drug products, including requirements pertaining to marketing and promotion of drugs in accordance with the provisions of the approved labeling and manufacturing of products in accordance with cGMP requirements. Violations of such requirements may lead to investigations alleging violations of the FDCA, and other statutes, including the False Claims Act and other federal and state health care fraud and abuse laws as well as state consumer protection laws.

For example, the FDA and other equivalent competent authorities in foreign jurisdictions strictly regulate the promotional claims that may be made about prescription products, such as setmelanotide, if approved. In particular, a product may not be promoted for uses that are not approved by the FDA or such other regulatory agencies as reflected in the product's approved labeling. If we receive marketing approval for setmelanotide as a treatment for obesity caused by certain genetic deficiencies affecting the MC4R pathway, physicians may nevertheless prescribe setmelanotide to their patients in a manner that is inconsistent with the approved labeling. If we are found to have promoted such off-label uses, we may become subject to significant liability. The federal government has levied large civil and criminal fines against companies for alleged improper promotion and has enjoined several companies from engaging in off-label promotion. The FDA has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed. Oversight and management of promotional practices may require operational changes and additions, if setmelanotide is approved and commercialized. If we cannot successfully manage the promotion of setmelanotide, if approved, we could become subject to significant liability, which would materially adversely affect our business and financial condition.

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

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

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

- The United States federal healthcare Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, or receiving remuneration, (anything of value), directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, lease order or arranging for or recommending the purchase, lease or order of any good or service for which payment may be made, in whole or in part, by federal healthcare programs such as Medicare and Medicaid. This statute has been interpreted to apply to arrangements between pharmaceutical companies

on one hand and prescribers, purchasers, formulary managers, and patients on the other. Liability under the Anti-Kickback Statute may be established without proving actual knowledge of the statute or specific intent to violate it. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. Although there are a number of statutory exceptions and regulatory safe harbors to the federal Anti-Kickback Statute protecting certain common business arrangements and activities from prosecution or regulatory sanctions, the exceptions and safe harbors are drawn narrowly. Practices that involve remuneration to those who prescribe, purchase, or recommend pharmaceutical and biological products, including certain discounts, or engaging such individuals or patients as consultants, advisors, or speakers, may be subject to scrutiny if they do not fit squarely within an exception or safe harbor. Our practices may not in all cases meet all of the criteria for safe harbor protection from anti-kickback liability. Moreover, there are no safe harbors for many common practices, such as educational and research grants, charitable donations, product and patient support programs. In October 2019, the federal government published a proposed regulation creating new safe harbors for, among other things, certain value-based arrangements and patient engagement tools, and that modifies and clarifies the scope of existing safe harbors for warranties and personal service agreements. The impact of the proposed regulation on our current or contemplated operations is not clear even if the proposed regulation is finalized.

- The federal civil False Claims Act prohibits individuals or entities from, among other things, knowingly presenting, or causing to be presented a false or fraudulent claim for payment of government funds, or knowingly making, using or causing to be made or used a false record or statement material to an obligation to pay money to the government or knowingly concealing or knowingly and improperly avoiding, decreasing or concealing an obligation to pay money to the federal government. Actions under the False Claims Act may be brought by the Attorney General or as a qui tam action by a private individual in the name of the government. Such private individuals may share in amounts paid by the entity to the government in recovery or settlement. Many pharmaceutical manufacturers have been investigated and have reached substantial financial settlements with the federal government under the civil False Claims Act for a variety of alleged improper activities including causing false claims to be submitted as a result of the marketing of their products for unapproved and thus non-reimbursable uses, inflating prices reported to private price publication services which are used to set drug payment rates under government healthcare programs, and other interactions with prescribers and other customers including those that may have affected their billing or coding practices and submission to the federal government. The government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. False Claims Act liability is potentially significant in the healthcare industry because the statute provides for treble damages and significant mandatory penalties per false or fraudulent claim or statement for violations. Because of the potential for large monetary exposure, healthcare and pharmaceutical companies often resolve allegations without admissions of liability for significant and material amounts to avoid the uncertainty of treble damages and per claim penalties that may be awarded in litigation proceedings. Settlements may require companies to enter into corporate integrity agreements with the government, which may impose substantial costs on companies to ensure compliance. Pharmaceutical and other healthcare companies also are subject to other federal false claims laws, including, among others, federal criminal healthcare fraud and false statement statutes that extend to non-government health benefit programs.
- The federal Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program, including private third-party payors, and also imposes obligations, with respect to safeguarding the privacy, security and transmission of individually identifiable health information. Penalties for failure to comply with a requirement of HIPAA vary significantly and include civil monetary penalties as well as criminal penalties for knowingly obtaining or disclosing individually identifiable health information in violation of HIPAA. The criminal penalties increase if the wrongful conduct involves false pretenses or the intent to sell, transfer or use identifiable health information for commercial advantage, personal gain or malicious harm. HIPAA also prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false,

fictitious or fraudulent statement or representation, or making or using any false writing or document knowing the same to contain any materially false, fictitious or fraudulent statement or entry in connection with the delivery of or payment for healthcare benefits, items or services. Similar to the federal healthcare Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it to have committed a violation. Pharmaceutical and other healthcare companies also are subject to state laws governing the privacy and security of health, genetic, sensitive condition and personally identifiable information, many of which enable a state attorney general to bring actions and provide private rights of action to consumers as enforcement mechanisms. There is also heightened sensitivity for minors' information, which may be subject to additional protections. Federal regulators, state attorneys general, and plaintiffs' attorneys have been and will likely continue to be active in this space.

- The federal Physician Payments Sunshine Act, implemented as the Open Payments Program, requires certain manufacturers of drugs, devices, biologics and medical supplies to report payments and other transfers of value to physicians for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report annually to the United States Department of Health and Human Services, Centers for Medicare and Medicaid Services, information related to physicians (defined to include doctors, dentists, optometrists, podiatrists, and chiropractors) and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Beginning in 2022, applicable manufacturers also will be required to report information regarding payments and transfers of value provided to physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, and certified nurse-midwives. Manufacturers must submit reports on or before the 90th day of each calendar year disclosing reportable payments made in the previous calendar year.
- Analogous state laws and regulations, such as state anti-kickback and false claims laws, which may apply to items or services reimbursed under Medicaid and other state programs or, in several states, regardless of the payer, including private insurers. Some state laws require pharmaceutical companies to report expenses relating to the marketing and promotion of pharmaceutical products and to report gifts and payments to individual health care providers in those states. Some of these states also prohibit certain marketing-related activities including the provision of gifts, meals, or other items to certain health care providers. Some states restrict the ability of manufacturers to offer co-pay support to patients for certain prescription drugs. Some states require the posting of information relating to clinical studies and their outcomes. Other states and cities require identification or licensing of sales representatives. In addition, several states require pharmaceutical companies to implement compliance programs or marketing codes of conduct.
- Similar restrictions are imposed on the promotion and marketing of medicinal products in the EU member states and other countries, including restrictions on interactions with healthcare professionals and requirements for public disclosure of payments made to physicians. Laws (including those governing promotion, marketing and anti-kickback provisions), industry regulations and professional codes of conduct often are strictly enforced. Even in those countries where we may decide not to directly promote or market our products, inappropriate activity by our international distribution partners could have implications for us.

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

It is possible that governmental authorities will conclude that our business practices do not comply with current or future statutes, regulations or case law involving applicable fraud and abuse, privacy, or other healthcare laws and regulations. If our operations, including our engagements with healthcare professionals, researchers and patients, or our disease awareness and/or patient identification initiatives including genetic testing programs, or anticipated activities to be conducted by our field teams, were found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to costly investigations, significant civil, criminal and administrative monetary

penalties, imprisonment, damages, fines, disgorgement, exclusion from government funded healthcare programs, such as Medicare and Medicaid, contractual damages, diminished profits and future earnings, and the curtailment or restructuring of our operations, any of which could substantially disrupt our operations or financial results. Although compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. Any action against us for violation of these laws or regulations, even if we successfully defend against it, could cause us to incur significant legal expenses and generate negative publicity, which could harm our financial condition and divert our management's attention from the operation of our business.

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

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with the regulations of the FDA and applicable non-U.S. regulators, provide accurate information to the FDA and applicable non-U.S. regulators, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee misconduct could also involve the improper use of, including trading on, information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter employee misconduct, and any precautions we take to detect and prevent this activity may be ineffective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions. Some of these laws and related risks are described under the risk factor *"We may be subject to federal and state healthcare laws and regulations. If we are unable to comply or have not fully complied with such laws and regulations, we could face criminal sanctions, damages, substantial civil penalties, reputational harm and diminished profits and future earnings"* of this Quarterly Report on Form 10-Q.

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

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

EU member states, Switzerland and other countries have also adopted data protection laws and regulations, which impose significant compliance obligations. In the EU, the collection and use of personal data, including health and genetic data, is governed by the provisions of the General Data Protection Regulation, or GDPR. The GDPR became effective on

May 25, 2018, repealing the Data Protection Directive and increasing our responsibility and liability in relation to the processing of personal data of EU subjects.

The GDPR, together with the national legislation of the EU member states 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, 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 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. Guidance on implementation and compliance practices are often updated or otherwise revised.

With respect to the transfer of personal data out of the EU, the GDPR provides that the transfer of personal data to countries that are not considered by the European Commission to provide an adequate level of data protection, including the United States, is permitted only on the basis of complying with specific legal steps, a number of which are subject to legal challenges.

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 have initiated in the EU before the GDPR entered into application could adversely impact the validity of 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 and entered into a transition period during which it will continue its ongoing and complex negotiations with the EU relating to the future trading relationship between the parties. Significant political and economic uncertainty remains about whether the terms of the relationship will differ materially from the terms before withdrawal, as well as about the possibility that a so-called "no deal" separation will occur if negotiations are not completed by the end of the transition period.

These developments have created significant uncertainty about the future relationship between the United Kingdom and the EU. Lack of clarity about future U.K. laws and regulations as the United Kingdom determines which EU-derived laws and regulations to replace or replicate as part of a withdrawal, including financial laws and regulations, tax and free trade agreements, intellectual property rights, supply chain logistics, environmental, health and safety laws and regulations, immigration laws and employment laws, could further decrease foreign direct investment in the United Kingdom, increase costs, depress economic activity and restrict our access to capital. These developments, or the perception that any of them could occur, have 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 U.K. 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 Preclinical Development and Clinical Development of RM-853

We have assumed sole responsibility for the global product development and commercialization of RM-853, which may distract our management team from pursuing regulatory approval of setmelanotide, and we may never complete preclinical development of RM-853 or file an IND with the FDA. Many of the risks we have faced in preclinical development and in clinical development of setmelanotide will also exist in preclinical development of RM-853 and clinical development, should we ever enter into clinical development of RM-853

In March 2018 we entered into a license agreement with Takeda Pharmaceutical Company Limited, which we refer to as Takeda, to develop and commercialize T-3525770, now known as RM-853. RM-853 is a potent, orally available ghrelin o-acyltransferase, or GOAT, inhibitor currently in preclinical development for PWS. Under the terms of the license agreement, we assumed sole responsibility for the global product development and commercialization of RM-853. This relationship may distract our management team from clinical development of setmelanotide and may require us to expend financial and other resources. PWS is a complex disease and companies have had difficulties in developing new therapies for PWS. In addition, many of the risks we have faced in preclinical development and in clinical development of setmelanotide will also exist in preclinical development of RM-853 and clinical development, should we ever enter into clinical development of RM-853, including, but not limited to:

- RM-853 may not succeed in preclinical toxicology studies or may not be accepted by the FDA under an IND;
- results from preclinical studies may not be predictive of later clinical trials of RM-853;
- Phase 1 studies may show that RM-853 has a significant toxicities or pharmacokinetics not supportive of proceeding in development;
- failures or delays in the commencement or completion of preclinical studies or clinical trials could result in increased costs to us and could delay, prevent or limit our ability to generate revenue and continue our business;
- RM-853 could cause undesirable side effects that could result in significant negative consequences, including the inability to enter clinical development or receive regulatory approval;
- experience by others suggest that PWS patients are high risk for adverse experiences and for this, and many other reasons, clinical trials in that population are extremely challenging;
- other risks related to regulatory approval, and if ever received, marketing and commercialization of RM-853;
- potential product liability exposure;
- an inability to protect our intellectual property related to RM-853;

- risks related to our dependence on third parties, including in manufacturing RM-853 and conducting preclinical studies and clinical trials of RM-853;
- the burden of complying with complex and changing foreign regulatory, tax, accounting and legal requirements; and
- competition from other therapies in development for the treatment of PWS may result in reduced availability of patients for our clinical studies, the possible requirement to achieve clinical meaningful efficacy above any treatment that is approved prior to RM-853, and the potential for increased scrutiny from payers related to the relative benefit of RM-853 versus other therapies should they be approved prior to RM-853.

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.

In January 2020, Keith M. Gottesdiener, M.D., resigned as our Chief Executive Officer and President and as a member of our board effective on March 27, 2020. Recruiting and retaining a new Chief Executive Officer will be critical to our success. We are searching for a new Chief Executive Officer but may face challenges in finding a suitable candidate, and we may face risks related to this and any other transitions in our executive leadership team. We anticipate that we will experience a transitional period until our new Chief Executive Officer is hired and fully integrated into their new role. We cannot provide any assurance that the transition in leadership will not result in a disruption that adversely impacts our business and employee morale.

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. 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. 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. 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. 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.

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.

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 17.0% of our outstanding voting stock as of March 31, 2020. As a result, if these stockholders were to choose to act together, they would be able to significantly influence all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these stockholders could significantly influence elections of directors, any amendments of our organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may feel are in your best interest as one of our stockholders.

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

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

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.

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 setmelanotide;
- announcements of new products, technologies, commercial relationships, acquisitions or other events by us or our competitors;
- the success or failure of other weight loss therapies and companies targeting rare diseases and orphan drug treatment;
- regulatory or legal developments in the United States and other countries;
- failure of setmelanotide, if approved, to achieve commercial success;
- fluctuations in stock market prices and trading volumes of similar companies;
- general market conditions and overall fluctuations in U.S. equity markets;
- variations in our quarterly operating results;
- changes in our financial guidance or securities analysts' estimates of our financial performance;

- changes in accounting principles;
- our ability to raise additional capital and the terms on which we can raise it;
- sales of large blocks of our common stock, including sales by our executive officers, directors and significant stockholders;
- additions or departures of key personnel;
- discussion of us or our stock price by the press and by online investor communities; and
- other risks and uncertainties described in these risk factors.

Our quarterly operating results may fluctuate significantly.

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

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

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

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

We have incurred substantial losses during our history and we do not expect to become profitable in the near future and may never achieve profitability. Under the Code, a corporation is generally allowed a deduction for net operating losses, or NOLs, carried over from a prior taxable year. Under the Code, we can carry forward certain NOLs of our subsidiaries 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, 2019, until such NOLs expire. NOLs arising in taxable years ending after December 31, 2019 are not subject to expiration. NOLs arising in taxable years beginning after December 31, 2019 may only be used to offset up to 80% of the corporation's taxable income computed without taking into account NOL deductions. Other unused tax attributes, such as research tax credits may also be carried forward to offset future taxable income, if any, until such credits are used or expire. As of December 31, 2019, we had approximately \$268.0 million and \$241.3 million of unused federal and state carryforwards of NOLs, respectively, and approximately \$6.4 million and \$1.9 million of unused federal and state carryforwards of research tax credits, respectively. Of the federal NOL carryforwards at December 31, 2019, \$194.8

million can be carried forward indefinitely. Additionally, as of December 31, 2019, we had federal orphan drug credits related to qualifying research of \$6.9 million.

If a corporation undergoes an “ownership change,” generally defined as a greater than 50% change by value in its equity ownership over a 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 our June 2018 and October 2019 public offerings may result 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. As a result, our ability to use carryovers of pre-change 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.

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.

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 March 31, 2020, we have 44,088,390 shares of common stock outstanding.

The holders of approximately 7.9 million shares of our common stock, or approximately 18% of our total outstanding common stock as of March 31, 2020, are entitled to rights with respect to the registration of their shares under the Securities Act of 1933, as amended, or the Securities Act, subject to vesting schedules. Registration of these shares under the Securities Act would result in the shares becoming 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 an “emerging growth company,” and as a result of the reduced disclosure and governance requirements applicable to emerging growth companies, our common stock may be less attractive to investors.

We are an “emerging growth company” as defined in the JOBS Act, and we intend to take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies including, but not limited to, not being required to comply with the auditor attestation requirements of

Section 404 of the Sarbanes-Oxley Act of 2002, as amended, or Section 404, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved. If we choose not to comply with the auditor attestation requirements of Section 404, our auditors will not be required to attest to the effectiveness of our internal control over financial reporting. As a result, investors may become less comfortable with the effectiveness of our internal controls and the risk that material weaknesses or other deficiencies in our internal controls go undetected or may increase. If we choose to provide reduced disclosures in our periodic reports and proxy statements while we are an emerging growth company, investors would have access to less information and analysis about our executive compensation, which may make it difficult for investors to evaluate our executive compensation practices. We cannot predict if investors will find our common stock less attractive because we will rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile. We may take advantage of these reporting exemptions until we are no longer an “emerging growth company.” We will remain an “emerging growth company” until the earlier of (1) December 31, 2022, (2) the last day of the fiscal year (a) in which we have total annual gross revenue of at least \$1.07 billion, or (b) in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeds \$700 million as of the last business day of our most recently completed second fiscal quarter, and (3) the date on which we have issued more than \$1.0 billion in non-convertible debt during the prior three-year period.

For as long as we remain an emerging growth company, we may take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not applicable to emerging growth companies as described in the preceding risk factor.

Even after we no longer qualify as an emerging growth company, we may still qualify as a “smaller reporting company” if the market value of our common stock held by non-affiliates is below \$250 million (or below \$700 million if our annual revenue is less than \$100 million) as of the last business day of our second fiscal quarter in any given year, which would allow us to take advantage of certain scaled disclosure requirements.

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, when required, 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. However, while we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. 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. If we identify one or more material weaknesses in our internal control over financial reporting, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements and have a negative effect on the trading price of our common stock.

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

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

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

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

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.

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 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 after we are no longer an emerging growth company, we 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.

We cannot predict or estimate the amount of additional costs we may incur or the timing of such costs. 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 continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

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, 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:

- any derivative action or proceeding brought on our behalf;
- any action asserting a claim of breach of fiduciary duty;
- any action asserting a claim against us arising under the DGCL, our certificate of incorporation or our bylaws; and
- any action asserting a claim against us that is governed by the internal-affairs doctrine.

This exclusive-forum provision 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. 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 this provision. If a court were to find this exclusive-forum provision in our 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. Nothing in our certificate of incorporation will preclude stockholders that assert claims under the Securities Act or the Exchange Act from bringing such claims in state or federal court, subject to applicable law.

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.			
3.2	Amended and Restated Bylaws.	S-1/A	9/25/2017	3.5
10.1*	Summary of Non-Employee Director Compensation Policy.			
10.2*	Offer Letter, dated December 21, 2017, by and between the Company and Hunter C. Smith.			
10.3*†	Amendment No. 1 to Development and Manufacturing and Services Agreement, dated as of February 20, 2020, by and between the Company and Corden Pharma Brussels S.A.			
31.1*	Certification of the Principal Executive Officer and 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 and Principal Financial Officer, as required by Section 906 of the Sarbanes-Oxley Act of 2002 (18 U.S.C. 1350).			
101.INS*	XBRL Instance Document.			
101.SCH*	XBRL Taxonomy Extension Schema Document.			
101.CAL*	XBRL Taxonomy Extension Calculation Linkbase Document.			
101.DEF*	XBRL Taxonomy Extension Definition Linkbase Document.			
101.LAB*	XBRL Taxonomy Extension Label Linkbase Document.			
101.PRE*	XBRL Taxonomy Extension Presentation Linkbase Document.			

* Filed herewith.

** Furnished herewith.

† Portions of this exhibit (indicated by asterisks) have been redacted in compliance with Item 601(b)(10)(iv) of Regulation S-K.

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: May 4, 2020

By: /s/ Hunter C. Smith

Name: Hunter C. Smith

Title: Chief Financial Officer, Treasurer and Secretary
and Interim President and Chief Executive Officer
(Principal Executive, Financial and Accounting
Officer)

**AMENDED AND RESTATED
CERTIFICATE OF INCORPORATION OF
RHYTHM PHARMACEUTICALS, INC.**

Rhythm Pharmaceuticals, Inc., a corporation organized and existing under the laws of the State of Delaware (the "Corporation"), **DOES HEREBY CERTIFY:**

FIRST: The name of the Corporation is "Rhythm Pharmaceuticals, Inc." The date of filing the original Certificate of Incorporation of the Corporation with the Secretary of State of the State of Delaware was February 26, 2013 under the name "Rhythm Metabolic, Inc."

SECOND: This Amended and Restated Certificate of Incorporation (this "Restated Certificate") has been duly approved by the Board of Directors of the Corporation.

THIRD: This Restated Certificate has been duly adopted by the stockholders of the Corporation in accordance with the provisions of Sections 228, 242 and 245 of the General Corporation Law of the State of Delaware (the "DGCL"), and notice thereof has been given in accordance with the provisions of Section 228 of the DGCL.

FOURTH: The Certificate of Incorporation of this Corporation is hereby amended, integrated and restated to read as follows:

ARTICLE ONE

The name of the Corporation is Rhythm Pharmaceuticals, Inc.

ARTICLE TWO

The address of the Corporation's registered office is 251 Little Falls Drive, in the City of Wilmington, New Castle County, Delaware 19808. The name of the registered agent at such address is Corporation Service Company.

ARTICLE THREE

The nature of the business or purpose of the Corporation is to engage in any lawful act or activity for which corporations may be organized under the DGCL.

ARTICLE FOUR

Section 1. Authorized Shares. The total number of shares of all classes of capital stock which the Corporation shall have authority to issue is One Hundred Thirty Million (130,000,000) shares, consisting of:

(a) One Hundred Twenty Million (120,000,000) shares of common stock, par value \$0.001 per share ("Common Stock"); and

(b) Ten Million (10,000,000) shares of undesignated preferred stock, par value \$0.001 per share (the "Preferred Stock").

Such stock may be issued from time to time by the Corporation for such consideration as may be fixed by the board of directors of the Corporation (the "Board of Directors"). The following is a statement of the powers, designations, preferences, privileges, and relative rights in respect of each class of capital stock of the Corporation.

Section 2. Common Stock.

(a) General. The voting, dividend and liquidation rights of the holders of Common Stock are subject to and qualified by the rights of the holders of Preferred Stock.

(b) Voting. Except as otherwise provided by the DGCL or this Restated Certificate and subject to the rights of holders of any series of Preferred Stock, all of the voting power of the stockholders of the Corporation shall be vested in the holders of the Common Stock, and each holder of Common Stock shall have one vote for each share held by such holder on all matters voted upon by the stockholders of the Corporation; provided, however, that, except as otherwise required by law, holders of Common Stock, as such, shall not be entitled to vote on any amendment to this Restated Certificate (or on any amendment to a certificate of designations of any series of Preferred Stock) that alters or changes the powers, preferences, rights or other terms of one or more outstanding series of Preferred Stock if the holders of such affected series of Preferred Stock are entitled to vote, either separately or together with the holders of one or more other such series, on such amendment pursuant to this Restated Certificate (or pursuant to a certificate of designations of any series of Preferred Stock) or pursuant to the DGCL. There shall be no cumulative voting.

(c) Dividends. Except as otherwise provided by the DGCL or this Restated Certificate, dividends may be declared and paid on the Common Stock from funds lawfully available therefor if, as and when determined by the Board of Directors and subject to any preferential dividend rights of any then outstanding shares of Preferred Stock.

(d) No Preemptive Rights. The holders of the Common Stock shall have no preemptive rights to subscribe for any shares of any class of stock of the Corporation whether now or hereafter authorized.

(e) No Conversion Rights. The Common Stock shall not be convertible into, or exchangeable for, shares of any other class or classes or of any other series of the same class of the Corporation's capital stock.

(f) Liquidation. Upon the dissolution or liquidation or winding up of the affairs of the Corporation, whether voluntary or involuntary, holders of Common Stock will be entitled to receive all assets of the Corporation available for distribution to its stockholders equally on a per share basis, subject to any preferential rights of any then outstanding shares of Preferred Stock and after payment or provision for payment of the Corporation's debts.

Section 3. Preferred Stock. To the fullest extent authorized by the DGCL, shares of Preferred Stock may be issued from time to time in one or more series, each of such series to have such powers, designations, preferences, and relative, participating, optional, or other special rights, if any, and such qualifications and restrictions, if any, as are stated or expressed in the resolution or resolutions of the Board of Directors providing for such series of Preferred Stock. Different series of Preferred Stock shall not be construed to constitute different classes of shares for the purposes of voting by classes unless expressly so provided in such resolution or resolutions.

Authority is hereby granted to the Board of Directors, acting by resolution or resolutions adopted at any time and from time to time, to create, provide for, designate and issue, out of the authorized but unissued shares of Preferred Stock, one or more series of Preferred Stock, and, in connection with the creation of any such series of Preferred Stock, to determine and fix the powers, designations, preferences, and relative, participating, optional, or other special rights, if any, and the qualifications and restrictions, if any, including without limitation dividend rights, conversion rights, voting rights (if any), redemption privileges, and liquidation preferences, of such series of Preferred Stock (which need not be uniform among series), all to the fullest extent now or hereafter permitted by the DGCL. Without limiting the generality of the foregoing, the resolution or resolutions providing for the creation or issuance of any series of Preferred Stock may provide that such series shall be superior to, rank equally with, or be junior to any other series of Preferred Stock, all to the fullest extent permitted by law. No resolution, vote, or consent of the holders of the capital stock of the Corporation shall be required in connection with the creation or issuance of any shares of any series of Preferred Stock authorized by and complying with the conditions of this Restated Certificate, the right to any such resolution, vote, or consent being expressly waived by all present and future holders of the capital stock of the Corporation.

Any resolution or resolutions adopted by the Board of Directors pursuant to the authority vested in them by this Section 3 of Article Four shall be set forth in a certificate of designation along with the number of shares of such series of Preferred Stock as to which the resolution or resolutions shall apply and such certificate shall be executed, acknowledged, filed, recorded, and shall become effective, in accordance with Section 103 of the DGCL. Unless otherwise provided in any such resolution or resolutions, the number of shares of any such series of Preferred Stock

to which such resolution or resolutions apply may be increased (but not above the total number of authorized shares of Preferred Stock) or decreased (but not below the number of shares of such series of Preferred Stock then outstanding) by a certificate likewise executed, acknowledged, filed and recorded, setting forth a statement that a specified increase or decrease therein has been authorized and directed by a resolution or resolutions likewise adopted by the Board of Directors. In case the number of such shares shall be decreased, the number of shares so specified in the certificate shall resume the status which they had prior to the adoption of the first resolution or resolutions. When no shares of any such series of Preferred Stock are outstanding, either because none were issued or because none remain outstanding, a certificate setting forth a resolution or resolutions adopted by the Board of Directors that none of the authorized shares of such series of Preferred Stock are outstanding, and that none will be issued subject to the certificate of designations previously filed with respect to such series of Preferred Stock, may be executed, acknowledged, filed and recorded in the same manner as previously described and it shall have the effect of eliminating from this Restated Certificate all matters set forth in the certificate of designations with respect to such series of Preferred Stock. If no shares of any such series of Preferred Stock established by a resolution or resolutions adopted by the Board of Directors have been issued, the voting powers, designations, preferences and relative, participating, optional or other rights, if any, with the qualifications, limitations or restrictions thereof, may be amended by a resolution or resolutions adopted by the Board of Directors. In the event of any such amendment, a certificate which (i) states that no shares of such series of Preferred Stock have been issued, (ii) sets forth the copy of the amending resolution or resolutions and (iii) if the designation of such series of Preferred Stock is being changed, indicates the original designation and the new designation, shall be executed, acknowledged, filed, recorded, and shall become effective, in accordance with Section 103 of the DGCL.

ARTICLE FIVE

The Corporation is to have perpetual existence.

ARTICLE SIX

Section 1. Classification of Directors. Effective as of the closing (the "IPO Closing") of the Corporation's first public offering of shares of Common Stock registered pursuant to the Securities Act of 1933, as amended, the Board of Directors shall be divided into three classes of directors, Class I, Class II, and Class III, such classes to be as nearly equal in number of directors as possible, having staggered three-year terms of office (except to the extent otherwise provided in the next sentence with respect to the initial terms of such classes of directors). The initial term of office of the directors of Class I shall expire as of the first annual meeting of the Corporation's stockholders following the IPO Closing; the initial term of office of the directors of Class II shall expire as of the second annual meeting of the Corporation's stockholders following the IPO Closing; and the initial term of office of the directors of Class III shall expire as of the third annual meeting of the Corporation's stockholders following the IPO Closing. At each annual meeting of stockholders of the Corporation after the IPO Closing, nominees will stand for election to succeed those directors whose terms are to expire as of such annual meeting of stockholders, and such nominees elected at such annual meeting of stockholders shall be elected for a term expiring at the third annual meeting of stockholders following their election. Directors shall hold office until the annual meeting of stockholders in which their term is scheduled to expire as set forth above in this Section 1 of Article Six and until their respective successors are duly elected or qualified or until their earlier death, incapacity, resignation or removal. Those directors already in office immediately prior to the IPO Closing shall be allocated among the three classes of directors contemplated under this Section 1 of Article Six pursuant to a resolution or resolutions adopted by the Board of Directors prior to the IPO Closing.

Section 2. Removal. Subject to the special rights of the holders of any series of Preferred Stock to elect directors, the directors of the Corporation may be removed only for cause by the affirmative vote of the holders of at least seventy-five percent (75%) of the outstanding shares of capital stock of the Corporation entitled to vote in the election of directors or class of directors, voting together as a single class, at a meeting of the stockholders called for that purpose.

Section 3. Vacancies. Except as the DGCL may otherwise require, any new directorships or vacancies in the Board of Directors, including new directorships resulting from any increase in the number of directors to serve in the Board of Directors and/or any unfilled vacancies by reason of death, resignation, disqualification, removal for

cause, failure to elect or otherwise with respect to any director, may be filled only by the vote of a majority of the remaining directors then in office, although less than a quorum, or by the sole remaining director.

Section 4. Number of Directors. Subject to the special rights of the holders of any series of Preferred Stock to elect directors, the number of directors which shall constitute the Board of Directors shall be fixed exclusively by the Board of Directors from time to time in accordance with the by-laws of the Corporation. No decrease in the number of directors constituting the whole board shall shorten the term of any incumbent director.

ARTICLE SEVEN

The Board of Directors shall have the power and authority: (i) to adopt, amend or repeal the Corporation's by-laws, subject to the power of the stockholders of the Corporation entitled to vote with respect thereto to make, alter, amend or repeal the by-laws; provided, that with respect to the powers of stockholders entitled to vote with respect thereto to make, alter, amend or repeal the by-laws, in addition to any other vote otherwise required by law, the affirmative vote of the holders of at least seventy-five percent (75%) of the outstanding shares of capital stock of the Corporation entitled to vote in the election of directors or class of directors, voting together as a single class, shall be required to make, alter, amend or repeal the by-laws of the Corporation; and (ii) to the full extent permitted or not prohibited by law, and without the consent of or other action by the stockholders, to authorize or create mortgages, pledges or other liens or encumbrances upon any or all of the assets, real, personal or mixed, and franchises of the Corporation, including after-acquired property, and to exercise all of the powers of the Corporation in connection therewith.

ARTICLE EIGHT

Except as otherwise provided for by any resolutions of the Board of Directors providing for the issuance of any series of Preferred Stock, effective as of the IPO Closing, any action required or permitted to be taken by the stockholders of the Corporation may be taken only at a duly called annual or special meeting of the stockholders in which such action is properly brought before such meeting, and not by written consent in lieu of such a meeting. Subject to any special rights of the holders of any series of Preferred Stock, and to the requirements of applicable law, special meetings of stockholders of the Corporation may be called only by or at the direction of the Board of Directors pursuant to a resolution adopted by a majority of the total number of directors. Any business transacted at any special meeting of stockholders shall be limited to matters relating to the purpose or purposes stated in the notice of meeting

ARTICLE NINE

The Corporation reserves the right to amend, alter, change or repeal any provision contained in this Restated Certificate, in the manner now or hereafter prescribed by the DGCL, and all rights conferred upon stockholders herein are granted subject to this reservation. Notwithstanding anything to the contrary contained in this Restated Certificate, and notwithstanding that a lesser percentage may be permitted from time to time by applicable law, the affirmative vote of the holders of at least seventy-five percent (75%) of the outstanding shares of capital stock of the Corporation entitled to vote in the election of directors or class of directors, voting together as a single class (in addition to any separate class vote that may in the future be required pursuant to the terms of any outstanding Preferred Stock), shall be required to amend or repeal the provisions of Articles Four (only to the extent it relates to the authority of the Board of Directors to issue shares of Preferred Stock in one or more series, the terms of which may be determined by the Board of Directors), Six, Seven, Eight, Nine, Ten, or Eleven of this Restated Certificate or to reduce the numbers of authorized shares of Common Stock or Preferred Stock.

ARTICLE TEN

Section 1. Limitation of Liability. To the fullest extent permitted by the DGCL as it now exists or may hereafter be amended (but, in the case of any such amendment, only to the extent that such amendment permits the Corporation to provide broader indemnification rights than permitted prior thereto), no director of the Corporation shall be personally liable to the Corporation or to any of its stockholders for monetary damages for breach of fiduciary duty as a director, notwithstanding any provision of law imposing such liability; provided, however, that to the extent required from time to time by applicable law, this Article Ten shall not eliminate or limit the liability of a

director, to the extent such liability is provided by applicable law, (i) for any breach of the director's duty of loyalty to the corporation or its stockholders, (ii) for acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law, (iii) under Section 174 of the DGCL, or (iv) for any transactions from which the director derived an improper personal benefit.

Section 2. Indemnification. The Corporation shall, to the fullest extent permitted by Section 145 of the DGCL and as further provided in the Corporation's by-laws, each as amended from time to time, indemnify each person who was or is a party or is threatened to be made a party to any threatened, pending or completed action, suit or proceeding, whether civil, criminal, administrative or investigative, by reason of the fact that such person is or was, or has agreed to become, a director or officer of the Corporation, or is or was serving, or has agreed to serve, at the request of the Corporation, as a director, officer or trustee of, or in a similar capacity with, another corporation, partnership, joint venture, trust or other enterprise (including any employee benefit plan), or by reason of any action alleged to have been taken or omitted in such capacity, against all expenses (including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably incurred by him or her or on his or her behalf in connection with such action, suit or proceeding and any appeal therefrom.

Indemnification may include payment by the Corporation of expenses in defending an action or proceeding in advance of the final disposition of such action or proceeding upon receipt of an undertaking by the person indemnified to repay such payment if it is ultimately determined that such person is not entitled to indemnification under this Article Ten, which undertaking may be accepted without reference to the financial ability of such person to make such repayment.

The Corporation shall not indemnify any such person seeking indemnification in connection with a proceeding (or part thereof) initiated by such person unless the initiation thereof was approved by the Board of Directors or except and to the extent otherwise permitted in the Corporation's by-laws or in an agreement between the Corporation and such person.

The indemnification rights provided in this Article Ten (i) shall not be deemed exclusive of any other rights to which those indemnified may be entitled under the Corporation's by-laws, any law, agreement or vote of stockholders or disinterested directors or otherwise, and (ii) shall inure to the benefit of the heirs, executors and administrators of such persons. The Corporation may, to the extent authorized from time to time by its Board of Directors, grant indemnification rights to other employees or agents of the Corporation or other persons serving the Corporation and such rights may be equivalent to, or greater or less than, those set forth in this Article Ten.

Section 3. Merger or Consolidation. For purposes of this Article Ten, references to the "Corporation" shall include, in addition to the resulting corporation, any constituent corporation (including any constituent of a constituent) absorbed in a consolidation or merger which, if its separate existence had continued, would have had power and authority to indemnify its directors, officers and employees or agents, so that any person who is or was a director, officer, employee or agent of such constituent corporation, or is or was serving at the request of such constituent corporation as a director, officer, employee or agent of another corporation, partnership, joint venture, trust or other enterprise, shall stand in the same position under this Article Ten with respect to the resulting or surviving corporation as he or she would have with respect to such constituent corporation if its separate existence had continued.

Section 4. Amendment or Repeal. No amendment to or repeal of this Article Ten shall apply to or have any effect on the liability or alleged liability of any director for or with respect to any acts or omissions of such director occurring prior to the effective date of such amendment or repeal.

ARTICLE ELEVEN

Unless the Corporation, as authorized by the Board of Directors, consents in writing to the selection of one or more alternative forums, the Court of Chancery of the State of Delaware shall be the sole and exclusive forum for a stockholder (including a beneficial owner) to bring (i) any derivative action or proceeding brought on behalf of the Corporation, (ii) any action asserting a claim of breach of a fiduciary duty owed by any director, officer or other employee of the Corporation to the Corporation or the Corporation's stockholders, (iii) any action asserting a claim against the Corporation arising pursuant to any provision of the DGCL or this Restated Certificate or the

Corporation's by-laws or (iv) any action asserting a claim against the Corporation, its directors, officers or employees governed by the internal affairs doctrine. Any person or entity purchasing or otherwise acquiring any interest in shares of capital stock of the Corporation (including, without limitation, shares of Common Stock) shall, and shall be deemed to, have notice of and to have consented to the provisions of this Article Eleven.

ARTICLE TWELVE

If any provision or provisions of this Restated Certificate shall be held to be invalid, illegal or unenforceable as applied to any circumstance for any reason whatsoever: (i) the validity, legality and enforceability of such provisions in any other circumstance and of the remaining provisions of this Restated Certificate (including, without limitation, each portion of any paragraph of this Restated Certificate containing any such provision held to be invalid, illegal or unenforceable that is not itself held to be invalid, illegal or unenforceable) shall not in any way be affected or impaired thereby and (ii) to the fullest extent possible, the provisions of this Restated Certificate (including, without limitation, each such portion of any paragraph of this Restated Certificate containing any such provision held to be invalid, illegal or unenforceable) shall be construed so as to permit the Corporation to protect its directors, officers, employees and agents from personal liability in respect of their good faith service to or for the benefit of the Corporation to the fullest extent permitted by law.

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

IN WITNESS WHEREOF, this Amended and Restated Certificate of Incorporation has been executed by a duly authorized officer of this Corporation on this 10th day of October, 2017.

RHYTHM PHARMACEUTICALS, INC.

By: /s/ Keith Gottesdiener
Name: Keith Gottesdiener
Title: Chief Executive Officer

[Signature Page to Amended and Restated Certificate of Incorporation of Rhythm Pharmaceuticals, Inc.]

Summary of Non-Employee Director Compensation Policy

Under the Company's non-employee director compensation policy, all non-employee directors will be paid an annual retainer fee of \$40,000 and such additional fees as are set forth in the following table. All payments will be made quarterly in arrears.

Non-Employee Director	Annual Fee
Lead Director	\$ 25,000
Non-Executive Chair	\$ 30,000
Chairman of the audit committee	\$ 15,000
Member of the audit committee (other than chairman)	\$ 7,500
Chairman of the compensation committee	\$ 12,000
Member of the compensation committee (other than chairman)	\$ 6,000
Chairman of the governance and nominating committee	\$ 8,000
Member of the governance and nominating committee (other than chairman)	\$ 4,000

Under the policy, each individual who is initially appointed or elected to the board of directors will be eligible to receive an option to purchase up to 37,000 shares of our common stock under the 2017 Equity Incentive Plan on the date he or she first becomes a non-employee director. These option grants will vest annually over a three-year period from the date of grant, subject to continued service as a non-employee director through that vesting date. In addition, on the date of the annual meeting of stockholders, each continuing non-employee director who has served on the board of directors for a minimum of six months will be eligible to receive an option grant to purchase up to 18,500 shares of our common stock, which will vest in full upon the earlier of the first anniversary of the date of grant or the date of the next annual meeting of stockholders. The exercise price for each of these option grants will be equal to the fair market value of our common stock on the date of grant. These new director grants and annual grants will be subject to approval by our board of directors at the time of grant. The share numbers set forth herein will be appropriately adjusted for any split or recapitalization of the Company's securities.



**Rhythm Pharmaceuticals, Inc. 500
Boylston Street - 11th Floor Boston,
MA 02116
Main Telephone: 617-585-2090
www.rhythmtx.com**

December 21, 2017
Hunter Smith
c/o Rhythm Pharmaceuticals, Inc.
500 Boylston Street, 11th Floor
Boston, MA 02116

Dear Hunter:

On behalf of Rhythm Pharmaceuticals, Inc., (the "Company" or "Rhythm"), I am pleased to set forth below the amended and restated terms of your employment with the Company. You and Rhythm previously were parties to the employment offer letter dated as of July 17, 2017, which was amended and restated on September 13, 2017. This second amended and restated employment offer letter amends and restates the terms of that September 13, 2017 offer letter in its entirety.

Employment. You are currently the Chief Financial Officer of the Company, beginning on July 31, 2017, and during the term of your employment with the Company, you will continue to hold the position and title of Chief Financial Officer, reporting to Keith Gottesdiener, CEO. During the term of your employment with the Company, you will be responsible for performing the duties associated with the position above or as the Company may otherwise assign to you. Your primary place of employment initially will be in the Company's offices located in 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.

Signing Bonus. Prior to the date of this letter, the Company has paid to you, and you have received, a one-time cash signing bonus of \$27,000, which signing bonus was taxable to you.

Base Salary. During your employment, your salary will be \$380,000 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, you will be eligible to earn an incentive bonus, based on your performance and the Company's performance, each during the applicable fiscal year, if your employment continues in good standing on the date of payment of such incentive bonus. Your target annual incentive bonus opportunity shall be 35% of your annualized base salary.

Equity Grant. Any existing grants of equity you have in the Company will be treated consistent with the terms of the applicable agreements under which such awards have been granted. You may be awarded additional equity grants from time to time in accordance with normal business practice and in the sole discretion of the Company's Board of Directors. The terms of any future equity grant will be consistent with any plan under which they are granted and the terms of the applicable agreement for the award(s).

Relocation Expenses Allowance. Rhythm agrees to pay you \$173,151.84 to reimburse you for travel, commuting, lodging and other relocation expenses (including moving your family to Boston if you decide to do so) for a period of two years commencing on January 1, 2018. Such \$173,151.84 will be paid to you by the Company in equal monthly installments of \$7,214.66 in accordance with the Company's ordinary payroll practices, beginning on the first payroll date following January 1, 2018 and continuing for a period of 24 months thereafter. You acknowledge that this relocation expenses allowance will be taxable to you.

Benefits. You may participate in any and all benefit programs that the Company establishes and makes available to its employees from time to time, subject to the terms and conditions of those programs. The Company's benefits programs are subject to change at any time in the Company's sole discretion.

Vacation. You will be entitled to annual paid vacation of four (4) weeks. Your accrual and use of vacation time will be pursuant to any vacation or time off policy the Company may establish or modify from time to time. The Company's vacation policy is subject to change at any time in the Company's sole discretion.

Outside Board Duties. You currently serve as an independent director of the NYSE listed multinational Genessee & Wyoming Inc. ("Genessee"), and as a member of its Governance/Nominating Committee. You may remain as a director of Genessee, provided that your duties in such director role shall not in any way interfere with your role and duties as Chief Financial Officer of, and commitments to, the Company which shall supersede and take priority in any and all respects. Moreover, you agree that you will not be permitted to take on any additional director, board observer, advisory, consulting, or other such roles or commitments without the express prior written consent of the Chief Executive Officer of the Company.

Severance. If the Company terminates your employment without Cause (as defined below) or you resign your employment with the Company for Good Reason (as defined below) (in either event, a "Qualifying Termination"), then, subject to your execution of a reasonable release acceptable to the Company (the "Release"), the expiration of any revocation period provided in the Release and your continued compliance with the terms of the NDA (as defined below), the Company will pay you an amount (the "Regular Severance Amount") equal to your then-current base salary rate for a period of six (6) months, provided that, (i) if any such Qualifying Termination occurs at any time after the IPO, if any, the Regular Severance Amount shall be an amount equal to your then-current base salary rate for a period of nine (9) months and (ii) if any such Qualifying Termination occurs on, or at any time prior to, the first anniversary of the start date of your employment with the Company (even if such first anniversary occurs after the IPO), the Regular Severance Amount shall be an amount equal to your then-current base salary rate for a period of twelve (12) months.

If there is a Qualifying Termination within the three (3) months immediately preceding or the twelve (12) months immediately following a Change of Control (as defined in the Company's 2015 Equity Incentive

Plan, as may be amended and in effect from time to time or succeeded or superseded by a successor equity incentive plan), then, subject to your execution of a Release following your Separation from Service (as defined below), the expiration of any revocation period provided in the Release and your continued compliance with the terms of the NDA, the Company will pay you in lieu of any Regular Severance Amount, an amount (the "Change of Control Severance Amount") equal to your then-current base salary rate for a period of twelve (12) months plus an amount equal to 100% of your then-applicable target annual incentive bonus.

Any severance amount to which you may be entitled under this letter will be paid in substantially equal installments in accordance with the Company's ordinary payroll practices, beginning on the first payroll date following the date that is either (i) sixty (60) days after the date of your Separation from Service or (ii) in the case of a Separation from Service that is a Qualifying Termination that occurs within three (3) months immediately preceding a Change of Control, sixty (60) days after such Change of Control, provided that, in the case of either of the foregoing clauses (i) and (ii), the Company, in its sole discretion, may have the option to pay any such severance amount to you as a lump sum. To be eligible for either the Regular Severance Amount or the Change of Control Severance Amount, as applicable, you must execute and deliver the Release to the Company and allow it to become effective within thirty (30) days of your Separation from Service or, if later, within thirty (30) days of a Change of Control giving rise to a Change of Control Severance Amount entitlement.

In addition, if following your Separation from Service, you are eligible for and timely elect continued medical insurance coverage pursuant to COBRA, the Company will reimburse you for the applicable premiums for you and your eligible dependents during the period commencing on the date of your Separation from Service and ending on the earlier to occur of (a) the final day of the applicable severance period and (b) the date you otherwise become ineligible for continued coverage under COBRA. Notwithstanding the foregoing, if the Company determines that it cannot provide such reimbursement of premiums to you without potentially violating applicable law, the Company shall not be obligated to make any such payments or reimbursements to you.

If the Qualifying Termination occurs 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 equity of the Company subject thereto. The foregoing provisions of this paragraph shall apply notwithstanding anything express or implied to the contrary in any agreement or award between you and the Company, or in any plan of the Company, that is applicable to such outstanding equity award.

Notwithstanding anything herein to the contrary, in the event that any compensation or benefit that constitutes "nonqualified deferred compensation" within the meaning of Section 409A of the Internal Revenue Code of 1986, as amended (the "Code"), becomes payable upon the occurrence of a Change of Control, such compensation or benefit shall not be paid unless such Change of Control constitutes a "change in control event" within the meaning of Section 409A of the Code.

If any payment or benefit you would receive under this letter, when combined with any other payment or benefit you receive pursuant to the termination of your employment with the Company ("Payment") would (i) constitute a "parachute payment" within the meaning of Section 280G of the Code, and (ii) but

for this sentence, be subject to the excise tax imposed by Section 4999 of the Code (the "Excise Tax"), then such Payment shall be either (x) the full amount of such Payment or (y) such lesser amount (with your choice of whether to reduce cash payments or stock option compensation or both) as would result in no portion of the Payment being subject to the Excise Tax, whichever of the foregoing amounts, taking into account the applicable federal, state and local employment taxes, income taxes and the Excise Tax results in your receipt, on an after-tax basis, of the greater amount of the Payment notwithstanding that all or some portion of the Payment may be subject to the Excise Tax.

Definitions

Separation from Service. For purposes of this letter, "Separation from Service" means a "separation from service" within the meaning of Section 409A of the Code. Each installment payment provided under this letter shall at all times be considered a separate and distinct payment for purposes of Section 409A of the Code. Notwithstanding anything in this letter to the contrary, to the extent required to avoid a prohibited distribution under Section 409A of the Code, the benefits provided under this letter will not be provided to you until the earlier of (a) the expiration of the six-month period measured from the date of your Separation from Service with the Company or (b) the date of your death. Upon the first business day after expiration of the relevant period, all payments delayed pursuant to the preceding sentence will be paid in a lump sum and any remaining payments due will be paid as otherwise provided herein.

Cause. "Cause" shall mean the occurrence of any of the following events by the individual: (i) commission of any crime involving the Company, or any crime involving fraud, breach of trust, or physical or emotional harm to any person, moral turpitude or dishonesty; (ii) any unauthorized use or disclosure of the Company's proprietary information (other than any such use or disclosure that is not intentional and is not material); (iii) any intentional misconduct or gross negligence that has a material adverse effect on the Company's business or reputation; (iv) any material breach by you of any agreement between you and the Company that is not cured within thirty (30) days after receipt of written notice from the Company describing any such breach; or (v) repeated and willful failure to perform the duties, functions and responsibilities of the individual's position after a written warning from the Company.

Good Reason. "Good Reason" shall mean your resignation from all positions you then hold with the Company if: (A) without your written consent (i) there is a material diminution in the nature or scope of your responsibilities, duties, authority, or title; (ii) there is a material reduction of your base salary; provided, however, that a material reduction in your base salary pursuant to a salary reduction program affecting all or substantially all of the employees of the Company and that does not adversely affect you to a greater extent than other similarly situated employees shall not constitute Good Reason; or (iii) you are required to relocate your primary work location to a facility or location that would increase your one way commute distance by more than thirty-five (35) miles from your primary work location as of immediately prior to such change, (B) you provide written notice outlining such conditions, acts or omissions to the Company's Chief Executive Officer, President, or General Counsel within thirty (30) days immediately following such material change or reduction, (C) such material change or reduction is not remedied by the Company within thirty (30) days following the Company's receipt of such written notice and (D) your resignation is effective not later than thirty (30) days after the expiration of such thirty (30) day cure period. "Good Reason" shall also mean your resignation, at your sole discretion, on the one year anniversary of a Change of Control from all positions you then hold with the Company or its

successor if by that date (i) you have not entered into a written letter or agreement with the Company or such successor that provides for your continued employment with the Company or such successor, and (ii) if at that one year anniversary of a Change of Control, another Chief Financial Officer has any control and/or oversight, directly or indirectly, over the Company (or what used to be the Company prior to such transaction). For purposes of clarification, any Qualifying Termination that occurs on the first anniversary of a Change of Control shall be deemed and treated as occurring within the twelve (12) months immediately following a Change of Control for all purposes of this letter.

Invention, Non-Disclosure, Non-Competition and Non-Solicitation Obligations. You previously have executed and delivered the Company's standard form of Employee Proprietary Information, Inventions, Non-Competition and Non-Solicitation Agreement (the "NDA"), an executed copy of which is attached hereto as Exhibit A.

At-Will Employment. This letter shall not be construed as an agreement, either express or implied, to employ you for any stated term, and shall in no way alter the Company's policy of employment at-will. Similarly, nothing in this letter shall be construed as an agreement, either express or implied, to pay you any compensation or grant you any benefit beyond the end of your employment with the Company, except as otherwise explicitly set forth in this letter. This letter supersedes all prior understandings, whether written or oral, including, without limitation, your current employment agreement, with respect to the subject matter of this letter.

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



Please indicate your acceptance of this letter agreement by signing below in the space provided for your signature.

Sincerely,
/S/ Keith Gottesdiener
Keith M. Gottesdiener
Chief Executive Officer

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

/S/Hunter Smith

January 22, 2018

Hunter Smith

Date



EXHIBIT

A EXECUTED

NDA

[See attached]

Certain information marked as [***] has been excluded from this exhibit because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

AMENDMENT NO. 1 TO DEVELOPMENT AND MANUFACTURING SERVICES AGREEMENT

Amendment No. 1 to Development and Manufacturing and Services Agreement dated as of February 20, 2020 (the “**Amendment**”), between RHYTHM PHARMACEUTICALS, INC., a Delaware corporation, located at 222 Berkeley Street, 12th Floor, Boston, MA 02116, f/k/a Rhythm Metabolics, Inc. (“**RHYTHM**”), and Corden Pharma Brussels S.A., a Belgian company located at Rue de Ransbeek 310, 1120 Bruxelles, successor-in-interest to Peptisyntha, Inc. (“**MANUFACTURER**,” and together with Rhythm, the “**Parties**”, and each, a “**Party**”).

WHEREAS, Rhythm and Peptisyntha Inc. have entered into a Development and Manufacturing and Services Agreement, effective as of July 17, 2013 (the “**Existing Agreement**”), which was assigned from Peptisyntha Inc. to Corden Pharma Brussels S.A. f/k/a Peptisyntha S.A.; and

WHEREAS, the Parties have entered into a Quality Agreement with an effective date of March 29, 2019 superseding all previous quality assurance agreements between them (the “**Quality Agreement**”); and

WHEREAS, the Parties hereto desire to amend the Existing Agreement to provide for the manufacture of Setmelanotide API lots by Manufacturer on the terms and subject to the conditions set forth herein; and

WHEREAS, pursuant to Section 15.6 of the Existing Agreement, the amendment contemplated by the Parties must be contained in a written agreement signed by an authorized representative of each Party.

NOW, THEREFORE, in consideration of the foregoing and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties agree as follows:

1. Definitions. Capitalized terms used and not defined in this Amendment have the respective meanings assigned to them in the Existing Agreement.
2. Amendment to the Existing Agreement. As of the Effective Date (defined below), the Existing Agreement is hereby amended or modified as follows:

Section 2.3 of the Existing Agreement is hereby amended by inserting at the end of such Section the following new Section 2.4:

2.4 Manufacture of Setmelanotide API.

- (a) Rhythm desires for Manufacturer to manufacture Setmelanotide API on behalf of Rhythm, and Manufacturer desires to perform such service. The Parties will enter into a Work Order that will set forth the material terms of that project (the “Setmelanotide Work Order”), and such Setmelanotide Work Order shall also be subject to the terms of the Existing Agreement, the Quality Agreement, and this Amendment, including, without limitation, the provisions of the milestone schedule attached to this Agreement as Appendix B (“Milestone Schedule”).
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Certain information marked as [***] has been excluded from this exhibit because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

- (b) Rhythm agrees to pay to Manufacturer the applicable success milestone payment set forth on the Milestone Schedule within [***] ([***)] days of the successful completion of each milestone as set forth in Appendix B. The successful completion of each milestone, as defined by the associated deliverable, and the determination of the date of completion shall be governed by the terms of the Existing Agreement and the Quality Agreement, and in particular Section 6 of the Existing Agreement (Testing and Acceptance Process), which – to the extent the respective Work Order covers the performance of Services which do not comprise Manufacturing of *Setmelanotide API* – may be applied *mutatis mutandis* for those Service deliverables as may be further described in the respective Work Order. The quality of the *Setmelanotide API* shall be in accordance with the respective mutually agreed specifications. Due to the nature of the timelines, Rhythm acknowledges that Manufacturer has to timely initiate performance of certain milestones even before preceding milestones are met. Thus, the commencement of a milestone may be independent of the completion of the preceding milestone, and each successfully completed milestone shall be paid for separately.
- (c) Rhythm agrees to fund [***] FTEs (as defined below) to be employed by Manufacturer with adequate skills and experience to undertake all tasks associated with the Setmelanotide Work Order. Each of the FTEs shall be dedicated to the Setmelanotide Work Order or other Services agreed upon by Rhythm and shall be fully supported by other site functions and staff of Manufacturer to complete the program. Manufacturer shall invoice Rhythm on a monthly basis commencing on [***] for the FTEs in an amount not to exceed [***] ([***)] per month. In addition, Manufacturer shall invoice Rhythm on or after [***] for a one-time FTE administrative fee in the amount of [***] ([***)). “FTE” means a full-time employee or equivalent individual having the appropriate skill and experience to conduct the specified activity and who is dedicated to the conduct of the specified activity a total of at least [***] ([***)] hours per week.
- (d) Notwithstanding Section 14.1 of the Existing Agreement, Rhythm, in Rhythm’s sole and absolute discretion, has the option to terminate the Setmelanotide Work Order and the payments for the FTEs described above at any time after the Effective Date of this Amendment. If Rhythm terminates the Setmelanotide Work Order, Rhythm shall reimburse Manufacturer for the expenses accrued under the Setmelanotide Work Order up to the time of termination and in addition the monthly costs for such FTEs for [***] following termination. If termination occurs between two milestones, then the payment will be for expenses incurred and fees for services initiated before the termination, but in no event shall Rhythm’s reimbursement obligation exceed the amount of fees (but not milestone payments) due at the completion of the milestone during which termination occurred. If Rhythm terminates the Setmelanotide Work Order, Manufacturer shall not be entitled to any other fees or additional milestone payments set forth on the Milestone Schedule for milestones subsequent to termination.

The Parties hereby agree to insert in Section 12 of the Existing Agreement the new Subsection 12.6 to read as follows:

12.6 FURTHER LIMITATION OF LIABILITY. SAVE FOR WRONGFUL INTENTIONAL ACTS OR OMISSIONS, EITHER PARTY’S LIABILITY UNDER THIS AGREEMENT

Certain information marked as [***] has been excluded from this exhibit because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

SHALL BE LIMITED TO THE AMOUNT OF [***] FOR ALL CLAIMS ARISING UNDER THIS AGREEMENT. NOTHING IN THIS SECTION 12.6 IS INTENDED TO LIMIT OR RESTRICT DAMAGES AS A RESULT OF A BREACH OF THE CONFIDENTIALITY AND NON-USE OBLIGATIONS IN SECTION 10.

The Parties hereby agree that the milestone schedule attached to this Amendment shall be attached to the Existing Agreement as new Appendix B.

3. Date of Effectiveness; Limited Effect. This Amendment will be deemed effective as of the date first written above (the “**Effective Date**”) and for the avoidance of doubt this Amendment shall also qualify as timely renewal of the Existing Agreement prior to the expiration of the then current term in accordance with Section 14.1 with the effect of a newly extended two year term until July 2021. Except as expressly provided in this Amendment, all of the terms and provisions of the Existing Agreement are and will remain in full force and effect and are hereby ratified and confirmed by the Parties. Without limiting the generality of the foregoing, the amendments contained herein will not be construed as an amendment to or waiver of any other provision of the Existing Agreement or as a waiver of or consent to any further or future action on the part of either Party that would require the waiver or consent of the other Party. On and after the Effective Date, each reference in the Existing Agreement to “this Agreement,” “the Agreement,” “hereunder,” “hereof,” “herein,” or words of like import will mean and be a reference to the Existing Agreement as amended by this Amendment.

4. Representations and Warranties. Each Party hereby represents and warrants to the other Party subject to the amended Section 12.6 of the Existing Agreement that:

- (a) It has the full right, power, and authority to enter into this Amendment and to perform its obligations hereunder and when entering into the Existing Agreement as amended by this Amendment each Party had the full right, power, and authority to enter into the Existing Agreement and to perform its obligations thereunder and each Party continues to have the full right, power, and authority to perform its obligations thereunder.
- (b) The execution of this Amendment by the individual whose signature is set forth at the end of this Amendment on behalf of such Party, and the delivery of this Amendment by such Party, have been duly authorized by all necessary action on the part of such Party.
- (c) This Amendment has been executed and delivered by such Party and (assuming due authorization, execution, and delivery by the other Party hereto) constitutes the legal, valid, and binding obligation of such Party, enforceable against such Party in accordance with its terms, except as may be limited by any applicable bankruptcy, insolvency, reorganization, moratorium, or similar laws and equitable principles related to or affecting creditors’ rights generally or the effect of general principles of equity.

5. Miscellaneous.

- (a) This Amendment is governed by and construed in accordance with the laws of the State of New York without regard to the conflict of laws provisions of such State.

Certain information marked as [***] has been excluded from this exhibit because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

- (b) This Amendment shall inure to the benefit of and be binding upon each of the Parties and each of their respective successors and assigns.
- (c) The headings in this Amendment are for reference only and do not affect the interpretation of this Amendment.
- (d) This Amendment may be executed in counterparts, each of which is deemed an original, but all of which constitute one and the same agreement. Delivery of an executed counterpart of this Amendment electronically or by facsimile shall be effective as delivery of an original executed counterpart of this Amendment.
- (e) This Amendment constitutes the sole and entire agreement between the Parties with respect to the subject matter contained herein, and supersedes all prior and contemporaneous understandings, agreements, representations, and warranties, both written and oral, with respect to such subject matter.
- (f) Each Party shall pay its own costs and expenses in connection with this Amendment (including the fees and expenses of its advisors, accountants, and legal counsel).
- (g) Time is of the essence with respect to any and all time periods for taking any action under this Amendment.

IN WITNESS WHEREOF, the Parties have executed this Amendment as of the date first written above.

RHYTHM PHARMACEUTICALS, INC.

By /s/ Hunter Smith
Name: Hunter Smith
Title: CFO

CORDEN PHARMA BRUSSELS S.A.

By /s/ Jan Braes
Name: Jan Braes
Title: Managing Director

Appendix B
Milestone Schedule to
Setmelanotide WORK ORDER

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: May 4, 2020

/s/ Hunter C. Smith

Name: Hunter C. Smith

Title: Chief Financial Officer and Interim President and
Chief Executive Officer
(principal executive officer and principal financial
officer)

**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, Hunter C. Smith, certify pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to my knowledge, the Quarterly Report on Form 10-Q of Rhythm Pharmaceuticals, Inc. for the fiscal quarter ended March 31, 2020 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 such Form 10-Q 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 Interim President and
Chief Executive Officer
(principal executive officer and principal financial
officer)

May 4, 2020
