REFINITIV

DELTA REPORT

10-Q

RYTM - RHYTHM PHARMACEUTICALS, I

10-Q - MARCH 31, 2023 COMPARED TO 10-Q - SEPTEMBER 30, 2022

The following comparison report has been automatically generated

TOTAL DELTAS	1742
CHANGES	204
DELETIONS	789
ADDITIONS	749

REFINITIV

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-Q

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

For the quarterly period ended September 30, 2022 March 31, 2023

OR

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

For the transition period from to

Commission file number 001-38223

RHYTHM PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

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

222 Berkeley Street

12th Floor

Boston, MA 02116

(Address of Principal Executive Offices)

(Zip Code)

(857) 264-4280

(Registrant's Telephone Number, Including Area Code)

N/A

(Former Name, Former Address and Former Fiscal Year, if Changed Since Last Report)

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

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

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15 (d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☐ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☐ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ☐ ☐	Accelerated filer ☐
Non-accelerated filer ☐ ☐	Smaller reporting company ☐☐
	Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

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

The number of shares outstanding of the registrant's Common Stock as of November 2, 2022 April 24, 2023 was 56,348,331. 56,854,940.

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RHYTHM PHARMACEUTICALS, INC.

FORM 10-Q

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PART I – FINANCIAL INFORMATION

Item 1. Financial Statements

Rhythm Pharmaceuticals, Inc.

Condensed Consolidated Balance Sheets

(in thousands, except share and per share data)

(Unaudited)

	September 30, 2022	December 31, 2021	March 31, 2023	December 31, 2022
Assets				
Current assets:				
Cash and cash equivalents	$ 185,087	$ 59,248	$ 109,661	$ 127,677
Short-term investments	162,708	235,607	184,921	205,611
Accounts receivable, net	3,328	1,025	8,117	6,224
Inventory			5,487	2,917
Prepaid expenses and other current assets	10,751	12,507	9,652	11,807
Total current assets	361,874	308,387	317,838	354,236
Property and equipment, net	2,426	2,813	2,001	2,197
Right-of-use asset	1,273	1,522	1,088	1,182
Intangible assets, net	8,097	4,658	7,669	7,883
Restricted cash	328	328	328	328
Other long-term assets	15,616	11,815	16,754	16,655
Total assets	$ 389,614	$ 329,523	$ 345,678	$ 382,481
Liabilities and stockholders' equity				
Current liabilities:				
Accounts payable	$ 4,933	$ 5,737	$ 13,347	$ 4,797
Accrued expenses and other current liabilities	25,741	30,084	30,549	32,894
Deferred revenue	1,760	7,000	1,428	1,434
Lease liability	664	606	705	684

Total current liabilities	33,098	43,427	46,029	39,809
Long-term liabilities:				
Deferred royalty obligation	72,961	—	77,520	75,810
Lease liability	1,440	1,945	1,076	1,260
Derivative liability	920	—	1,290	1,340
Total liabilities	108,419	45,372	125,915	118,219
Stockholders' equity:				
Preferred Stock, $0.001 par value: 10,000,000 shares authorized; no shares issued and outstanding at September 30, 2022 and December 31, 2021	—	—		
Common stock, $0.001 par value: 120,000,000 shares authorized; 55,756,256 and 50,283,574 shares issued and outstanding at September 30, 2022 and December 31, 2021, respectively	56	50		
Preferred Stock, $0.001 par value: 10,000,000 shares authorized; no shares issued and outstanding at March 31, 2023 and December 31, 2022			—	—
Common stock, $0.001 par value: 120,000,000 shares authorized; 56,852,404 and 56,612,429 shares issued and outstanding at March 31, 2023 and December 31, 2022, respectively			56	56
Additional paid-in capital	949,043	813,041	981,950	974,356
Accumulated other comprehensive loss	(339)	(1)	(6)	(92)
Accumulated deficit	(667,565)	(528,939)	(762,237)	(710,058)
Total stockholders' equity	281,195	284,151	219,763	264,262
Total liabilities and stockholders' equity	$ 389,614	$ 329,523	$ 345,678	$ 382,481

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

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Rhythm Pharmaceuticals, Inc.

Condensed Consolidated Statements of Operations and Comprehensive Loss

(in thousands, except share and per share data)

(Unaudited)

	Three months ended September 30,		Nine months ended September 30,		Three months ended March 31,	
	2022	2021	2022	2021	2023	2022
Revenues:						
Product revenue, net	$ 4,284	$ 1,028	$ 8,094	$ 1,337	$ 11,469	$ 1,498
License revenue	—	—	6,754	—		
Costs and expenses:						

Cost of sales	497	222	1,105	363	1,421	230
Research and development	21,116	27,539	85,082	72,554	37,945	32,510
Selling, general, and administrative	21,938	17,507	65,715	47,490	24,634	21,449
Total costs and expenses	43,551	45,268	151,902	120,407	64,000	54,189
Loss from operations	(39,267)	(44,240)	(137,054)	(119,070)	(52,531)	(52,691)
Other income:						
Other expense	(370)	—	(370)	100,000		
Other expense, net					(27)	(233)
Interest expense	(2,144)	—	(2,190)	—	(3,061)	—
Interest income	920	138	988	313	3,440	160
Total other (expense) income, net	(1,594)	138	(1,572)	100,313		
Loss before taxes	(40,861)	(44,102)	(138,626)	(18,757)		
(Benefit from) provision for income taxes	—	(8,995)	—	7,989		
Total other income (expense), net					352	(73)
Net loss	$ (40,861)	$ (35,107)	$ (138,626)	$ (26,746)	$ (52,179)	$ (52,764)
Net loss per share, basic and diluted	$ (0.79)	$ (0.70)	$ (2.73)	$ (0.54)	$ (0.92)	$ (1.05)
Weighted-average common shares outstanding, basic and diluted	51,400,922	50,246,303	50,712,452	49,374,336	56,708,975	50,326,627
Other comprehensive loss:						
Net loss	$ (40,861)	$ (35,107)	$ (138,626)	$ (26,746)	$ (52,179)	$ (52,764)
Reclassification of losses on RareStone equity into net loss	300	—	—	—		
Foreign currency translation adjustment					21	—
Unrealized gain (loss), net on marketable securities	267	—	(338)	(107)	65	(628)
Comprehensive loss	$ (40,294)	$ (35,107)	$ (138,964)	$ (26,853)	$ (52,093)	$ (53,392)

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

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Rhythm Pharmaceuticals, Inc.

Condensed Consolidated Statements of Stockholders' Equity

(in thousands, except share data)

(Unaudited)

	Common Stock		Additional Paid-In	Accumulated Other Comprehensive	Accumulated	Total Stockholders'
	Shares	Amount	Capital	Income (Loss)	Deficit	Equity
Balance at December 31, 2021	50,283,574	$ 50	$ 813,041	$ (1)	$ (528,939)	$ 284,151
Balance at December 31, 2022	56,612,429	$ 56	$ 974,356	$ (92)	$ (710,058)	$ 264
Stock-based compensation expense	—	—	6,376	—	—	6
Issuance of common stock in connection with ESPP	32,169	—	665	—	—	
Issuance of common stock in connection with exercise of stock options and vesting of restricted stock units	207,806	—	553	—	—	
Foreign currency translation adjustment	—	—	—	21	—	
Unrealized gain on marketable securities	—	—	—	65	—	
Net loss	—	—	—		(52,179)	(52
Balance at March 31, 2023	56,852,404	$ 56	$ 981,950	$ (6)	$ (762,237)	$ 219

Stock-based compensation expense	—	—	4,611	—	—	4,611	—	—	4,611	—	—	4
Issuance of common stock in connection with ESPP	61,518	—	399	—	—	399	61,518	—	399	—	—	
Issuance of common stock in connection with exercise of stock options and vesting of restricted stock units	48,639	—	—	—	—	—	48,639	—	—	—	—	
Unrealized loss on marketable securities	—	—	—	(628)	—	(628)	—	—	—	(628)	—	
Net loss	—	—	—	—	(52,764)	(52,764)	—	—	—	—	(52,764)	(52
Balance at March 31, 2022	50,393,731	50	818,051	(629)	(581,703)	235,769	50,393,731	50	$ 818,051	$ (629)	$ (581,703)	$ 235
Stock-based compensation expense	—	—	5,137	—	—	5,137						
Issuance of common stock in connection with exercise of stock options and vesting of restricted stock units	60,439	—	—	—	—	—						
Unrealized gain on marketable securities	—	—	—	23	—	23						
Unrealized loss on RareStone equity	—	—	—	(300)	—	(300)						
Net loss	—	—	—	—	(45,001)	(45,001)						
Balance at June 30, 2022	50,454,170	50	823,188	(906)	(626,704)	195,628						
Stock compensation expense	—	—	4,796	—	—	4,796						
Issuance of common stock in connection with ESPP	31,414	—	227	—	—	227						

Issuance of common stock in connection with exercise of stock options and vesting of restricted stock units	470,672	1	3,863	—	—	3,864
Issuance of common stock upon completion of public offering, net of offering costs	4,800,000	5	116,969	—	—	116,974
Unrealized gain on marketable securities	—	—	—	267	—	267
Reclassification of losses on RareStone equity into net loss	—	—	—	300	—	300
Net loss	—	—	—	—	(40,861)	(40,861)
Balance at September 30, 2022	55,756,256	$ 56	$ 949,043	$ (339)	$ (667,565)	$ 281,195
Balance at December 31, 2020	44,235,903	$ 44	$ 625,762	$ 49	$ (459,327)	$ 166,528
Stock-based compensation expense	—	—	5,191	—	—	5,191
Issuance of common stock in connection with ESPP	17,000	—	388	—	—	388
Issuance of common stock in connection with exercise of stock options and vesting of restricted stock units	198,855	—	3,466	—	—	3,466
Issuance of common stock upon completion of public offering, net of offering costs	5,750,000	6	161,725	—	—	161,731

Unrealized loss on marketable securities	—	—	—	(107)	—	(107)
Net income	—	—	—	—	43,750	43,750
Balance at March 31, 2021	50,201,758	50	796,532	(58)	(415,577)	380,947
Stock compensation expense	—	—	5,669	—	—	5,669
Issuance of common stock in connection with exercise of stock options	24,981	—	383	—	—	383
Unrealized gain on marketable securities	—	—	—	79	—	79
Net loss	—	—	—	—	(35,389)	(35,389)
Balance at June 30, 2021	50,226,739	50	802,584	21	(450,966)	351,689
Stock compensation expense	—	—	5,268	—	—	5,268
Issuance of common stock in connection with ESPP	21,051		233			233
Issuance of common stock in connection with exercise of stock options	20,522	—	180	—	—	180
Net loss	—	—	—	—	(35,107)	(35,107)
Balance at September 30, 2021	50,268,312	$ 50	$ 808,265	$ 21	$ (486,073)	$ 322,263

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

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Condensed Consolidated Statements of Cash Flows

(in thousands)

(Unaudited)

	Nine months ended September 30,	
	2022	2021
Operating activities		
Net loss	$ (138,626)	$ (26,746)
Adjustments to reconcile net loss to net cash used in operating activities:		
Stock-based compensation expense	14,544	16,128
Gain on sale of priority review voucher	—	(100,000)
Deferred tax provision	—	7,989
Depreciation and amortization	1,230	833
Non-cash interest expense and amortization of debt issuance costs	2,190	—
Non-cash rent expense	(198)	(185)
Loss on RareStone equity investment	1,040	—
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	(1,072)	1,591
Deferred revenue	474	—
Other long-term assets	(4,841)	(10,533)
Accounts payable, accrued expenses and other current liabilities	(14,169)	5,392
Net cash used in operating activities	(139,428)	(105,531)
Investing activities		
Purchases of short-term investments	(151,521)	(456,238)
Maturities of short-term investments	224,607	292,197
Proceeds from sale of priority review voucher	—	100,000
Payment of milestone obligation under license agreement	(4,000)	(5,000)
Purchases of property and equipment	(282)	(366)
Net cash provided by (used in) investing activities	68,804	(69,407)
Financing activities		
Net proceeds from issuance of common stock	116,974	161,731
Proceeds from the exercise of stock options	3,863	4,029
Proceeds from issuance of common stock from ESPP	626	621
Proceeds from royalty financing agreement	75,000	—
Net cash provided by financing activities	196,463	166,381
Net increase (decrease) in cash, cash equivalents and restricted cash	125,839	(8,557)
Cash, cash equivalents and restricted cash at beginning of period	59,576	101,257
Cash, cash equivalents and restricted cash at end of period	$ 185,415	$ 92,700
Supplemental disclosures:		
Deferred financing costs in accrued expenses	$ 957	—

	Three months ended March 31,	
	2023	2022
Operating activities		
Net loss	$ (52,179)	$ (52,764)

Adjustments to reconcile net loss to net cash used in operating activities:		
Stock-based compensation expense	6,376	4,611
Depreciation and amortization	457	350
Non-cash interest expense and amortization of debt issuance costs	3,061	—
Non-cash rent expense	94	(65)
Change in fair value of embedded derivative liability	(50)	—
Acquired IPR&D assets classified as investing activities	5,395	—
Changes in operating assets and liabilities:		
Accounts receivable	(1,893)	—
Inventory	(2,570)	—
Prepaid expenses and other current assets	(186)	950
Deferred revenue	(6)	—
Other long-term assets	(99)	(6,661)
Accounts payable, accrued expenses and other liabilities	5,167	(53)
Net cash used in operating activities	(36,433)	(53,632)
Investing activities		
Purchases of short-term investments	(69,644)	(39,479)
Maturities of short-term investments	92,675	112,128
Acquisition of IPR&D assets, including transaction costs	(4,520)	—
Purchases of property and equipment	(47)	(127)
Net cash provided by investing activities	18,464	72,522
Financing activities		
Repayment of deferred royalty obligation	(1,351)	—
Proceeds from the exercise of stock options	553	—
Proceeds from issuance of common stock from ESPP	665	399
Net cash (used in) provided by financing activities	(133)	399
Effect of exchange rates on cash	86	—
Net (decrease) increase in cash, cash equivalents and restricted cash	(18,016)	19,289
Cash, cash equivalents and restricted cash at beginning of period	128,005	59,576
Cash, cash equivalents and restricted cash at end of period	$ 109,989	$ 78,865
Supplemental disclosure of non-cash investing activities:		
Holdback payable associated with the acquisition, in accrued expenses	$ 500	$ —
Transaction costs associated with the acquisition, in accounts payable	$ 375	$ —

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

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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 global, commercial-stage biopharmaceutical company committed dedicated to transforming the lives of patients and their families living with rare diseases. We are focused on advancing our lead asset, IMCIVREE® (setmelanotide), as a precision medicine designed to treat hyperphagia and severe obesity caused by rare melanocortin-4 receptor (MC4R) pathway diseases. Rhythm's precision medicine, While obesity affects hundreds of millions of people worldwide, we are advancing IMCIVREE® (setmelanotide), for a subset of individuals who have hyperphagia, a pathological hunger, and severe obesity due to an impaired MC4R pathway, which may be caused by traumatic injury or genetic variants. The MC4R pathway is an endocrine pathway in the brain that is responsible for regulating hunger, caloric intake and energy expenditure, which consequently affect body weight. IMCIVREE, an MC4R agonist for which we have exclusive hold worldwide rights, has is 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. In the United States, IMCIVREE first-ever therapy developed for patients with certain ultra-rare diseases that is approved for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndromic obesity due to pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency as determined by U.S. Food and Drug Administration (FDA) approved test demonstrating variants in *POMC*, *PCSK1* or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance, or Bardet-Biedl syndrome (BBS). The European Commission (EC) has authorized setmelanotide for the treatment of obesity and the control of hunger associated with genetically confirmed BBS or genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. The UK's Medicines & Healthcare Products Regulatory Agency (MHRA) authorized setmelanotide for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. In addition, we are advancing a broad clinical development program for setmelanotide in patients with hyperphagia and severe obesity caused by additional rare MC4R pathway diseases to expand the approved indications in the United States and Europe. In addition to the United States, (US), European Union (EU) and United Kingdom, we and our partners are seeking approval and market access for IMCIVREE to treat patients with these MC4R pathway-related obesities in Argentina and Israel. Great Britain.

The Company is a Delaware corporation organized in February 2013 under the name Rhythm Metabolic, Inc., and as of October 2015, under the name Rhythm Pharmaceuticals, Inc. The Company has wholly owned subsidiaries in the United States, US, Ireland, the United Kingdom, France, Italy, the Netherlands, France, Germany, Italy, Spain and Canada.

The Company is subject to risks and uncertainties common to commercial-stage companies in the biotechnology industry, including but not limited to, risks associated with the commercialization of approved products, completing preclinical studies and clinical trials, receiving regulatory approvals for product candidates, development by competitors of new biopharmaceutical products, dependence on key personnel, protection of proprietary technology, compliance with government regulations and the ability to secure additional capital to fund operations. Commercialization of approved products will require significant resources and in order to market IMCIVREE, the Company must continue to build its sales, marketing, managerial and other non-technical capabilities or make arrangements with third parties to perform these services. Product candidates currently under development will require significant additional research and development efforts, including preclinical and clinical testing and regulatory approval, prior to commercialization. These efforts require significant amounts of additional capital, adequate personnel and infrastructure and extensive compliance-reporting capabilities.

There are many uncertainties regarding the COVID-19 pandemic, and the Company is closely monitoring the impact of the pandemic on all aspects of its business, including how the pandemic may continue to impact its patients, employees, suppliers, vendors, business partners and distribution channels. While the pandemic did not materially affect the Company's financial results and business operations for the three and nine months ended September 30, 2022 March 31, 2023, the Company is unable to predict the impact that COVID-19 will have on its financial position and operating results in future periods

due to numerous uncertainties. The Company will continue to assess the evolving impact of the COVID-19 pandemic and will make adjustments to its operations as necessary.

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Liquidity

The Company has incurred operating losses and negative cash flows from operations since inception. As of September 30, 2022 March 31, 2023, the Company had an accumulated deficit of $667,565. $762,237. The Company has primarily funded these losses through the proceeds from the sales of common and preferred stock, asset sales, royalty financing, out-license arrangements, as well as capital contributions received from the former parent company, Rhythm Holdings LLC. To date, the Company has minimal product revenue and management expects operating losses to continue for the foreseeable future. The Company has devoted substantially all of its resources to its drug development efforts, comprising of research and development, manufacturing, conducting clinical trials for its product candidates, protecting its intellectual property, commercialization activities and general and administrative functions relating to these operations. The future success of

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the Company is dependent on its ability to develop its product candidates and ultimately upon its ability to attain profitable operations.

At September 30, 2022 March 31, 2023, the Company had $347,795 $294,582 of cash and cash equivalents and short-term investments on hand. In the future, the Company will be dependent on obtaining funding from third parties, such as proceeds from the issuance of debt, sale of equity, product sales and funded research and development programs to maintain the Company's operations and meet the Company's obligations. There is no guarantee that additional equity or other financings will be available to the Company on acceptable terms, or at all. If the Company fails to obtain additional funding when needed, the Company would be forced to scale back, terminate its operations or seek to merge with or be acquired by another company. Management believes that the Company's existing cash and cash equivalents and short-term investments will be sufficient to fund the Company's operations into 2025.through at least the next twelve months from the filing of this Quarterly Report on Form 10-Q with the SEC.

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 condensed consolidated balance sheet as of September 30, 2022 March 31, 2023, the condensed consolidated statements of operations and comprehensive (loss) income loss for the three and nine months ended September 30, 2022 March 31, 2023 and 2021, 2022, the condensed consolidated statements of stockholders' equity for the three and nine months ended September 30, 2022 March 31, 2023 and 2021 2022 and the condensed consolidated statements of cash flows for the nine three months ended September 30, 2022 March 31, 2023 and 2021 2022 and the related footnote disclosures are unaudited. In management's opinion, the unaudited condensed consolidated financial statements have been prepared on the same basis as the audited consolidated financial statements as of and for the year ended December 31, 2021 December 31, 2022 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 and nine months ended September 30, 2022 March 31, 2023 are not necessarily indicative of the results expected for the full fiscal year, any other interim periods, or any future year or period.

The accompanying unaudited condensed consolidated financial statements reflect the application of certain significant accounting policies as described below and elsewhere in these notes to the unaudited condensed consolidated financial statements. As of September 30, 2022 March 31, 2023, 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, 2021 December 31, 2022.

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Use of Estimates

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent liabilities at the date of the financial statements and the reported amounts of revenue and expenses during the reporting period. The Company bases its estimates on historical experience and other market-specific or other relevant assumptions that it believes to be reasonable under the circumstances. This process may result in actual results differing materially from those estimated amounts used in the preparation of the financial statements if these results differ from historical experience, or other assumptions do not turn out to be substantially accurate, even if such assumptions are reasonable when made. Significant estimates relied upon in preparing these financial statements include estimates related to determining our net product revenue, license revenue, accruals related to research and development expenses, assumptions used to record stock-based compensation expense, interest expense on our deferred royalty obligation, assumptions used to value the embedded derivative in our deferred royalty obligation, assumptions used to value the common stock received from RareStone Group

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Ltd., or RareStone, and the valuation allowance on the Company's deferred tax assets. Estimates are periodically reviewed in light of changes in circumstances, facts and experience. Changes in estimates are recorded in the period in which they become known. Actual results could differ materially from those estimates.

Principles of Consolidation

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

Reclassification of Prior Year Balances

Certain prior year amounts have been reclassified to conform to the current period presentation. These reclassifications had no effect on the reported results of operations or cash flows. Specifically, in the condensed consolidated statement of operations and comprehensive loss for the three months ended March 31, 2022, the Company has reclassified $160 of interest income which was previously recorded within other (expense) income, net to interest income.

Segment Information

Operating segments are defined as components of an entity about which separate discrete information is available for evaluation by the chief operating decision maker, or decision-making group, in deciding how to allocate resources and in assessing performance. The Company currently operates in one business segment, which is the development and commercialization of therapies for patients with rare diseases. A single management team that reports to the Chief Executive Officer comprehensively manages the entire business. The Company does not operate separate lines of business with respect to its product or product candidates. Accordingly, the Company has one reportable segment.

Off-Balance Sheet Risk and Concentrations of Credit Risk

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

The Company is exposed to risks associated with extending credit to customers related to the sale of products. The Company does not require collateral to secure amounts due from its customers. At September 30, 2022 As of March 31, 2023 and December 31, 2022, approximately 86% 83% and 85% of all of the Company's revenue was generated from a single customer in the United States.

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

Segment Information

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

business segment, which is the development United States and commercialization Europe, respectively. The inability of therapies the vendor to fulfill testing services for patients with rare diseases. A single management team that reports to the Chief Executive Officer comprehensively manages the entire business. The Company does not operate separate lines of business with respect to its product or product candidates. Accordingly, the Company has one reportable segment. could materially impact future operating results and adversely impact our ability to further develop setmelanotide. A change in the relationship with the genetic testing service providers, or an adverse change in their business, could materially impact future operating results.

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Accounts Receivable, net

Accounts receivable consists of amounts due from customers, net of customer allowances for cash discounts and any estimated expected credit losses. The Company's measurement of expected credit losses is based on relevant information about past events, including historical experience, current conditions, and reasonable and supportable forecasts

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that affect the collectability of the reported amount. To date, the Company has not experienced any credit losses. The Company's contracts with its customers have standard customary payment terms that generally require payment within 45 90 days. The Company analyzes amounts that are past due for collectability, and periodically evaluates the creditworthiness of its customers. At September 30, 2022 As of March 31, 2023 and December 31, 2022, the Company determined an allowance for doubtful account was not required based upon our review of contractual payments and our customers' circumstances.

Revenue Recognition

We recognize The Company recognizes revenue in accordance with Accounting Standards Codification ASC Topic 606,*Revenue from Contracts with Customers*, or ASC 606, which applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements, and financial instruments. 606. Under ASC 606, we recognize an entity recognizes revenue when our its customer obtains control of promised goods or services in an amount that reflects the consideration which we expect the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that we determine are within the scope of ASC 606, we perform the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) we satisfy a performance obligation. At contract inception, once the contract is determined to be within the scope of ASC 606, the Company assesses the goods or services promised within each contract and determines those that are performance obligations and assesses whether each promised good or service is distinct. We then recognize as

revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

Product Revenue, net

Subsequent to its regulatory approval, the Company began to sell IMCIVREE in In the United States in March 2021 and in France and Germany in March 2022 and June 2022, respectively. (the "U.S."), which accounts for the largest portion of our total revenues, the Company sells its product to a limited number of specialty pharmacies. The product is distributed through an exclusive third-party logistics, or 3PL, distribution agent that does not take title to the product. Once the product is delivered to the Company's exclusive specialty pharmacy provider, our sole customer in the U.S., the customer or wholesaler (or "wholesaler") takes title to the product. The wholesaler then distributes the product to health care providers and patients. In our exclusive distribution agreement with the 3PL company, the Company acts as principal because we retain control of the product. Internationally, we make sales primarily to specialty distributors and retail pharmacy chains, as well as hospitals, many of which are government-owned or supported. The Company generally does not offer returns of product sold to the customer.

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

Reserves for Variable Consideration

Revenues from product sales are recorded at the net sales price, or the transaction price, which includes estimates of variable consideration for which reserves are established and which result from discounts, returns, chargebacks, rebates, co-pay assistance and other allowances that are offered within contracts between us and our customers, health care providers and other indirect customers relating to the sale of IMCIVREE. These reserves are based on the amounts earned or to be claimed on the related sales and are classified as reductions of accounts receivable (if the amount is payable to the customer) or a current liability (if the amount is payable to a party other than a customer). Where appropriate, these estimates take into consideration a range of possible outcomes that are probability-weighted for relevant factors such as

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our historical experience, current contractual and statutory requirements, specific known market events and trends, industry data and forecasted customer buying and payment patterns. Overall, these reserves reflect our best estimates of the amount of consideration to which we are entitled based on the terms of the contract. The amount of variable consideration that is included in the transaction price may be constrained and is included in the net sales price only to the extent that it is

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considered probable that a significant reversal in the amount of the cumulative revenue recognized will not occur in a future period. Actual amounts of consideration ultimately received may differ from our estimates. If actual results in the future vary from our estimates, we will adjust these estimates, which would affect net product revenue and earnings in the period such variances become known.

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

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

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

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

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

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

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

During the three and nine months ended September 30, 2022 March 31, 2023 and 2021, 2022, we recorded product revenue, net, of $4,284, $1,028, $8,094, $11,469 and $1,337, $1,498, respectively. The table that summarizes balances and activity in each of the product revenue allowance and reserve categories has not been included for the three and nine months ended September 30, 2022 March 31, 2023 due to the immateriality of the revenue recognized during the periods.

License Agreements

We generate revenue from license or similar agreements with pharmaceutical companies for the development and commercialization of certain of our products and product candidates. Such agreements may include the transfer of intellectual property rights in the form of licenses, transfer of technological know-how, delivery of drug substances,

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research and development services, and participation on certain committees with the counterparty. Payments made by the customers may include non-refundable upfront fees, payments upon the exercise of customer options, payments based upon the achievement of defined milestones, and royalties on sales of products and product candidates if they are approved and commercialized.

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

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

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

When consideration is received, or such consideration is unconditionally due, from a customer prior to transferring goods or services to the customer under the terms of a contract, a contract liability is recorded within deferred revenue.

Contract liabilities within deferred revenue are recognized as revenue after control of the goods or services is transferred to the customer and all revenue recognition criteria have been met.

For arrangements that include sales-based royalties, including sales-based milestone payments, and a license of intellectual property that is deemed to be the predominant item to which the royalties relate, we recognize revenue at the later of when the related sales occur or when the performance obligation to which some or all of the royalties have been allocated has been satisfied (or partially satisfied).

RareStone Group Ltd.

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

According to the terms of the RareStone License, RareStone has agreed to seek local approvals to commercialize IMCIVREE for the treatment of obesity and hyperphagia due to biallelic POMC, PCSK1 or LEPR deficiency, as well as Bardet-Biedl and Alström syndromes. Additionally, RareStone has agreed to fund efforts to identify and enroll patients from China in the Company's global EMANATE trial, a Phase 3, randomized, double-blind, placebo-controlled trial to

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

As of March 31, 2022, the The Company initially estimated the fair value of the RareStone equity to be $2,440 based on a preliminary valuation. valuation during the first quarter of 2022. Upon completion of the valuation procedures during the three month period ended June 30, 2022, second quarter of 2022, the Company concluded the initial fair value of the RareStone equity to be $1,040. The $1,400 change in fair value upon finalizing our valuation During the third quarter of the RareStone equity resulted in an adjustment to the contract liability account within our condensed consolidated financial statements for the three and six months ended June 30, 2022. At September 30, 2022, 2022, the Company estimated the fair value of the RareStone equity to be de minimis based upon the results of an updated valuation. The Company also valuation and recorded an other-than-temporary impairment of $1,040 related to the decline in fair value as a component of other expense in our condensed consolidated statements of operations and other comprehensive loss for the three and nine month periods year ended September 30, 2022, respectively. December 31, 2022 (recorded in the third quarter of 2022). The other-than-temporary impairment of $1,040 included the reclassification of a $300 unrealized loss previously recorded as a component of accumulated

other comprehensive income (loss) in our condensed consolidated statement of stockholders' equity during the second quarter of 2022.

The Company received total upfront consideration of $8,040 comprised of an upfront payment of $7,000, and the estimated fair value of the RareStone equity of $1,040. The Company determined that the RareStone License contains two performance obligations, the delivery of the license and the supply of clinical and commercial product. The Company further determined the supply of commercial product to RareStone contains a significant future discount and estimates the discount to be $1,286, which is recorded as a component of deferred revenue on the condensed consolidated balance sheet at September 30, 2022. The discount related to commercial manufacturing supply will be deferred March 31, 2023 and recognized over the commercial supply period. December 31,2022.

Based on a relative fair-value allocation between the license and the manufacture of clinical and commercial product, the Company recognized $6,754 of license revenue in the consolidated statements of operations and comprehensive loss during the nine months year ended September 30, 2022. As December 31, 2022 (recorded in the second quarter of 2022 upon the Company fulfilled fulfilling its obligations in transferring the license to RareStone during RareStone). The discount related to commercial manufacturing supply will be deferred and recognized over the second quarter commercial supply period or upon termination of 2022 no the agreement. No license revenue was recognized during the three-month periods ended March 31, 2023 or 2022, respectively.

On October 28, 2022, we delivered written notice, or the Notice, to RareStone that we have terminated the RareStone License for cause. In accordance with the three month period ended September 30, 2022. Notice, we maintain that RareStone has materially breached its obligations under the RareStone License to fund, perform or seek certain key clinical studies and waivers, including with respect to our global EMANATE trial, among other obligations. On December 21, 2022, RareStone provided written notice to us that it objects to the claims in the Notice, including our termination of the RareStone License for cause. On March 16, 2023, we provided written notice to RareStone reaffirming our position that RareStone has materially breached its obligations under the RareStone License and that we have terminated the RareStone License for cause, and also requested documentation supporting RareStone's purported dispute notice objecting to the claims in the Notice. RareStone may attempt to cure the alleged breaches, which the Company believe to be incurable, within the timeframe specified under the RareStone License.

Deferred Royalty Obligation

We treat The Company treats the debt obligation to HealthCare Royalty Management, LLC as discussed further in Note 10, 12, "Long-term Obligations", as a deferred royalty obligation, amortized using the effective interest rate method over the estimated life of the revenue streams. We recognize The Company recognizes interest expense thereon using the effective rate, which is based on our current estimates of future revenues over the life of the arrangement. In connection therewith, we the Company periodically assess our assesses its expected revenues using internal projections, impute imputes interest on the carrying value of the deferred royalty obligation, and record records interest expense using the imputed effective interest rate. To the extent our the Company's estimates of future revenues are greater or less than previous estimates or the estimated timing of such payments is materially different than previous estimates, we the Company will account for any such changes by adjusting the effective interest rate on a prospective basis, with a corresponding impact to the reclassification of our deferred royalty obligation. The assumptions used in determining the expected repayment term of the deferred royalty obligation and amortization

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period of the issuance costs requires that we the Company to make estimates that could impact the short-term and long-term classification of such costs, as well as the period over which such costs will be amortized.

Cost of Product Sales Inventory

Prior to receiving approval from the FDA in November 2020 to sell IMCIVREE in the United States, the Company expensed all costs incurred related to the manufacture of IMCIVREE as research and development expense because of the inherent risks associated with the development of a drug candidate, the uncertainty about the regulatory approval process and the lack of history for the Company of regulatory approval of drug candidates. Subsequent The Company values inventories at the lower of cost or estimated net realizable value. The Company determines the cost of inventories, which includes amounts related to receiving FDA approval materials and manufacturing overhead, on a first-in, first-out basis. Raw materials and work in November 2020, process includes all inventory costs prior to packaging and labelling, including raw materials, active pharmaceutical ingredient, and drug product. Finished goods include packaged and labelled products. Raw materials and work in process that may be used for either research and development or commercial sale are classified as inventory until the Company has capitalized a nominal amount material is consumed or otherwise allocated for research and development. If the material is intended to be used for research and development, it is expensed as research and development once that determination is made.

Cost of inventory related costs that

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were incurred subsequent to FDA approval. At September 30, 2022, the Company had $1,575 of inventory recorded as a component of prepaid and other current assets on the condensed consolidated balance sheet.

Cost of product sales will consist consists of manufacturing costs, transportation and freight, amortization of capitalized intangibles, royalty payments and indirect overhead costs associated with the manufacturing and distribution of IMCIVREE. Cost of product sales may also include periodic costs related to certain manufacturing services and inventory adjustment charges. Finally, cost of sales may also include costs related to excess or obsolete inventory adjustment charges, abnormal costs, unabsorbed manufacturing and overhead costs, and manufacturing variances.

Intangible Assets, Net

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

Impairment of Long-Lived Assets

The Company evaluates its long-lived assets, which consist primarily of property and equipment and finite lived intangible assets, for impairment whenever events or changes in circumstances indicate that the carrying amount of such assets may not be recoverable. Factors that the Company considers in deciding when to perform an impairment review include significant underperformance of the business in relation to expectations, significant negative industry or economic trends and significant changes or planned changes in the use of the assets. The Company measures recoverability of assets to be held and

used by comparing the carrying amount of an asset to the future undiscounted net cash flows expected to be generated by the asset. If such assets are considered to be impaired, the Company measures the impairment to be recognized by the amount by which the carrying amount of the asset exceeds the fair value of the asset, less the cost to sell. No events or changes in circumstances existed to require an impairment assessment during the three or nine months ended September 30, 2022 March 31, 2023 and 2021, 2022, respectively.

Acquired IPR&D and Milestones Expenses

In an asset acquisition, payments incurred prior to regulatory approval to acquire rights to in-process research and development projects are expensed as acquired IPR&D and recorded as a component of research and development expense in the condensed consolidated statements of operations and comprehensive net loss unless the project has an alternative future use. These costs include upfront and development milestone payments related to licensing arrangements, or other asset acquisitions that provide rights to develop, manufacture and/or sell pharmaceutical products. Where contingent development milestone payments are due to third parties, prior to regulatory approval, the payment obligations are expensed when the milestone results are achieved. Regulatory and commercial milestone payments made to third parties

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subsequent to regulatory approval are capitalized as intangible assets and amortized to cost of products sold over the remaining useful life of the related product.

Foreign Currency Translation

The functional currencies of the Company's foreign subsidiaries are Euros and British pound sterling. Foreign subsidiary earnings are translated into U.S. dollars using average exchange rates. The net assets of foreign subsidiaries are translated into U.S. dollars using period-end exchange rates. The U.S. dollar effects that arise from translating the net assets of these subsidiaries at changing rates are recognized in other comprehensive income (loss) in the condensed consolidated statements of operations and comprehensive loss.

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, derivative liability and RareStone equity at September 30, 2022 March 31, 2023 and December 31, 2021 December 31, 2022 were carried at fair value, determined according to the fair value hierarchy. See Note 4 6 for further discussion.

The carrying amounts reflected in the consolidated balance sheets for accounts payable and accrued expenses and other current liabilities approximate their fair values due to their short-term maturities at September 30, 2022 March 31, 2023 and December 31, 2021 December 31, 2022, respectively.

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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, performance stock units 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 is the same for all periods presented.

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The following table includes the potential common shares that were excluded from the computation of diluted net loss per share as their effect would have been anti-dilutive for the periods indicated:

	Three Months Ended September 30,	Nine Months Ended September 30,	Three Months Ended March 31,

	2022	2021	2022	2021	2023	2022
Stock options	6,584,725	5,966,664	6,584,725	5,966,664	6,973,369	7,248,111
Restricted stock units	726,080	439,957	726,080	439,957	1,046,232	784,041
Performance stock units	811,128	—	811,128	—	613,191	935,885
Potential common shares	8,121,933	6,406,621	8,121,933	6,406,621	8,632,792	8,968,037

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.

On October 18, 2022, the Company completed the sale of 580,000 shares of common stock at a price to the public of $26.00 per share, pursuant to the partial exercise of the underwriters' option to purchase up to an additional 720,000 shares in connection with its public offering of 4,800,000 shares of common stock that closed on September 19, 2022. The Company received aggregate net proceeds from the partial option exercise of approximately $14,175, after deducting underwriting discounts and commissions and offering expenses payable by the Company.

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.

3. Asset Acquisition

Xinvento B.V.

On February 27, 2023, the Company, through its wholly-owned Dutch subsidiary, Rhythm Pharmaceuticals Netherlands B.V., a Dutch private limited liability company ("Rhythm BV"), entered into a Share Purchase Agreement (the "Purchase Agreement") with Xinvento B.V., a Dutch private limited liability company based in the Netherlands ("Xinvento"), and the other parties named therein, pursuant to which, and concurrently with the execution thereof, Rhythm BV acquired all of the issued and outstanding shares of Xinvento. The aggregate consideration at closing was approximately $5,400, inclusive of transaction costs, as adjusted pursuant to the terms of the Purchase Agreement and subject to the distribution and payment terms set forth therein (the "Closing Purchase Price").

In addition to the Closing Purchase Price, the Purchase Agreement provides for the payment of additional contingent consideration totaling up to $206,000 upon achievement of certain development, regulatory and commercial milestones by Xinvento, as follows: (i) up to an aggregate of $6,000 in clinical development milestones; (ii) up to an aggregate of $125,000 in regulatory approval and commercial milestones; and (iii) up to an aggregate of $75,000 in sales milestones in the event a second molecule is selected, developed and approved.

The total purchase consideration of $5,400 was composed of $4,520 of cash paid at closing, a $500 holdback, payable on the one-year anniversary of the acquisition, and $375 of acquisition-related costs. The Company determined that substantially all of the value as of acquisition date related to Xinvento's In-Process Research and Development. As a result, the Company determined this transaction should be accounted for as an asset acquisition.

The assets acquired were In-Process Research and Development (IPR&D) assets. However, since the IPR&D assets were determined to have no alternative future use, the Company recognized the $5,400 of purchase consideration as research and development expense in the three months ended March 31, 2023.

The Company determined that the additional contingent consideration did not meet the definition of a derivative as of the acquisition date. Therefore, the Company did not record a contingent consideration liability on the acquisition date. The

Company will recognize any future contingent consideration payments related to the Xinvento transaction in the period in which the achievement of the underlying milestones becomes probable.

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Xinvento's results of operations are included in the condensed consolidated financial statements from the date of acquisition. For the three months ended March 31, 2023, the net loss associated with the operations of Xinvento were de-minimis in the Company's condensed consolidated statements of operations.

4. Inventory

Inventory consists of the following:

	March 31, 2023	December 31, 2022
Raw Materials	$ 4,696	$ 2,722
WIP	—	—
Finished Goods	791	195
Total Inventory	$ 5,487	$ 2,917

3. 5. Accrued Expenses and Other Current Liabilities

Accrued expenses and other current liabilities consisted of the following:

	September 30, 2022	December 31, 2021	March 31, 2023	December 31, 2022
Research and development costs	$ 9,192	$ 17,480	$ 13,956	$ 11,379
Professional fees	2,879	2,163	3,417	4,502
Payroll related	8,482	8,371	5,501	11,444
Deferred financing fees	957	—		
Royalties	215	791	586	440
Sales Allowances			4,265	2,710
Other	4,016	1,279	2,824	2,419
Accrued expenses and other current liabilities	$ 25,741	$ 30,084	$ 30,549	$ 32,894

6. Fair Value of Financial Assets and Liabilities

As of March 31, 2023 and December 31, 2022, the carrying amount of cash and cash equivalents and short-term investments was $294,582 and $333,288, respectively, which approximates fair value. Cash and cash equivalents and short-term investments includes investments in U.S. treasury securities and money market funds that invest in U.S. government securities that are valued using quoted market prices. Accordingly, money market funds and government funds are categorized as Level 1. The financial assets valued based on Level 2 inputs consist of corporate debt securities and commercial paper, which consist of investments in highly-rated investment-grade corporations.

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4. Fair Value of Financial Assets

As of September 30, 2022 and December 31, 2021, the carrying amount of cash and cash equivalents and short-term investments was $347,795 and $294,855, respectively, which approximates fair value. Cash and cash equivalents and short-term investments includes investments in U.S. treasury securities and money market funds that invest in U.S. government securities that are valued using quoted market prices. Accordingly, money market funds and government funds are categorized as Level 1. The financial assets valued based on Level 2 inputs consist of corporate debt securities and commercial paper, which consist of investments in highly-rated investment-grade corporations.

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

	Fair value Measurements as of September 30, 2022 using:				Fair Value Measurements as of March 31, 2023 using:			
	Level 1	Level 2	Level 3	Total	Level 1	Level 2	Level 3	Total
Assets:								
Cash Equivalents:								
Commercial Paper	$ —	$ 34,028	$ —	$ 34,028				
Money Market Funds	115,208	—	—	115,208				
Marketable Securities:								
Corporate Debt Securities and Commercial Paper	—	162,708	—	162,708				
Cash equivalents:								
Money market funds					$83,773	$ —	$ —	$ 83,773
Marketable securities:								
Corporate debt securities and commercial paper					—	184,921	—	184,921
Total	$ 115,208	$ 196,736	$ —	$ 311,944	$83,773	$184,921	$ —	$268,694
Liabilities:								
Derivative on Royalty Financing	$ —	$ —	$ 920	$ 920				
Derivative liability					$ —	$ —	$1,290	$ 1,290
Total	$ —	$ —	$ 920	$ 920	$ —	$ —	$1,290	$ 1,290

	Fair value Measurements as of December 31, 2021 using:				Fair Value Measurements as of December 31, 2022 using:			
	Level 1	Level 2	Level 3	Total	Level 1	Level 2	Level 3	Total
Assets:								
Cash Equivalents:								
Corporate Debt Securities and Commercial Paper	$ —	$ —	$ —	$ —				
Money Market Funds	48,297	—	—	48,297				
Marketable Securities:								
Corporate Debt Securities and Commercial Paper	—	235,607	—	235,607				
Cash equivalents:								
Commercial paper					$ —	$ 8,484	$ —	$ 8,484
Money market funds					99,962	—	—	99,962
Marketable securities:								
Corporate debt securities and commercial paper					—	205,611	—	205,611
Total	$ 48,297	$ 235,607	$ —	$ 283,904	$99,962	$214,095	$ —	$314,057
Liabilities:								
Derivative liability					$ —	$ —	$1,340	$ 1,340
Total					—	—	1,340	1,340

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

The embedded derivative liability associated with our deferred royalty obligation, as discussed further in Note 10, 12, "Long-Term Obligations", is measured at fair value using an option pricing Monte Carlo simulation model and is included as a component of the deferred royalty obligation. The embedded derivative liability is subject to remeasurement at the end of each reporting period, with changes in fair value recognized as a component of other (expense) income, net. The assumptions used in the option pricing Monte Carlo simulation model include: (1) our estimates of the probability and timing of related events; (2) the probability-weighted net sales of IMCIVREE, including worldwide net product sales, upfront payments, milestones and royalties; (3) our risk-adjusted discount rate that includes a company specific risk premium; (4) our cost of debt; (5) volatility; and (6) the probability of a change in control occurring during the term of the instrument.

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Our RareStone equity was valued at a de minimis amount and as such written-off at September 30, 2022. The Company determined the estimated fair values using a discounted cash flow model under the income approach and an option pricing allocation model for the period ended September 30, 2022. Inherent in discounted cash flow and option pricing allocation models are assumptions related to the equity value of the entity, expected equity volatility, holding period, risk-free interest rate and discount for lack of marketability. The Company estimated equity volatility based on historical volatility of guideline public companies. The risk-free interest rate was based on the U.S. Treasury rates for a maturity similar to the expected holding period.

Changes in our level 3 securities for the three months ended September 30, 2022 and 2021 are as follows:

	Nine months ended September 30,	
	2022	2021
Beginning aggregate estimated fair value of Level 3 securities	$ —	$ —
Initial recording of RareStone equity	1,040	—
Total realized and unrealized losses		
Realized loss included in other expense	(1,040)	—
Ending aggregate estimated fair value of Level 3 securities	$ —	$ —

	Three months ended March 31,	
	2023	2022
Beginning aggregate estimated fair value of Level 3 RareStone equity	$ —	$ —
Initial recording of RareStone equity	—	2,440
Change in fair value of embedded derivative	—	—
Ending aggregate estimated fair value of Level 3 RareStone equity	$ —	$ 2,440

	Three months ended March 31,	
	2023	2022
Beginning aggregate estimated fair value of Level 3 liabilities	$ 1,340	$ —
Change in fair value of embedded derivative	(50)	—
Ending aggregate estimated fair value of Level 3 liabilities	$ 1,290	$ —

Marketable Securities

The following tables summarize the Company's marketable securities:

	September 30, 2022				March 31, 2023			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Assets								
Corporate debt securities and commercial paper (due within 1 year)	$ 163,047	$ —	$ (339)	$ 162,708	$184,948	$ —	$ (27)	$184,921
	$ 163,047	$ —	$ (339)	$ 162,708	$184,948	$ —	$ (27)	$184,921

	December 31, 2021				December 31, 2022			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Assets								
Corporate debt securities and commercial paper (due within 1 year)	$ 235,608	$ 50	$ (51)	$ 235,607	$205,702	$ —	$ (91)	$205,611
	$ 235,608	$ 50	$ (51)	$ 235,607	$205,702	$ —	$ (91)	$205,611

5. 7. Right Of of Use Asset and Lease Liability

The Company has a material operating lease for its head office facility and other immaterial operating leases for certain equipment. The Company's office lease has a remaining lease term of 2.8 2.3 years. The Company measured the lease liability associated with the office lease using a discount rate of 10% at inception. The Company estimated the incremental borrowing rate for the leased asset based on a range of comparable interest rates the Company would incur to borrow an amount equal to the lease payments on a collateralized basis over a similar term in a similar economic environment. As of September 30, 2022 March 31, 2023, the Company has not entered into any lease arrangements classified as a finance lease.

The Company's corporate headquarters is located in Boston, Massachusetts. This facility houses the Company's research, clinical, regulatory, commercial and administrative personnel. The Company's lease agreement commenced May 2019 and has a term of six years with a five-year renewal option to extend the lease. The Company has not included the five-year renewal option to extend the lease in its measurement of the right-of-use asset or lease liability.

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The following table presents the maturities of the Company's operating lease liability related to office space as of September 30, 2022 March 31, 2023, all of which is under a non-cancellable operating lease:

	Operating Lease	Operating Lease
2022	$ 207	
2023	834	$ 627
2024	851	851
2025	502	502
Thereafter	—	—
Total operating lease payments	2,394	1,980
Less: imputed interest	290	(199)

Total operating lease liability	$ 2,104	$ 1,781

6. 8. Intangible Assets Net

	Estimated life (years)	As of March 31, 2023 Cost	Accumulated Amortization	Net	As of December 31, 2022 Cost	Accumulated Amortization	Net
Capitalized Milestones	11	$ 9,000	$ (1,331)	$ 7,669	$ 9,000	$ (1,117)	$ 7,883

As of September 30, 2022 March 31, 2023, the Company's finite-lived net intangible assets, which totaled $8,097 $7,669 resulted from the capitalization of certain milestone payments made to Ipsen Pharma, S.A.S., or Ipsen, in accordance with the terms of the Company's license agreement with Ipsen, in connection with the Company's first commercial sale of IMCIVREE in the U.S. in March 2021 and in France in March 2022.

As of September 30, 2022 March 31, 2023, amortization expense for the next five years and beyond is summarized as follows:

2022	$ 214	
2023	855	$ 641
2024	855	855
2025	855	855
2026	855	855
2027		855
Thereafter	4,463	3,608
Total	$ 8,097	$7,669

The Company began amortizing its finite-lived intangible assets in April 2021 over an 11 year period based on IMCIVREE's expected patent exclusivity period. Amortization expense totaled $214 $114, $560, and $228 $130 for the three and nine months ended September 30, 2022, March 31, 2023 and 2021, 2022, respectively Amortization expense is included in cost of sales in the condensed consolidated statements of operations and comprehensive loss.

7. 9. Income Taxes

The Company did not record a an income tax provision for the three and nine months ended September 30, 2022 March 31, 2023 and 2022, respectively as the Company generated sufficient tax losses during the period. The Company recorded a tax benefit of $8,995 and recorded a tax provision of $7,989 for the three and nine month periods ended September 30, 2021, respectively, primarily related to the sale of the Rare Pediatric Disease Priority Review Voucher, or PRV, offset by a tax benefit from ordinary losses generated by the Company during the period. The Company expects to have generate sufficient tax losses in the current year to offset income and thus no current year liability is expected. The Company expects to maintain a full valuation allowance against its net deferred tax assets for the year.

8. 10. Common Stock

As of September 30, 2022 March 31, 2023, an aggregate of 12,798,790 14,547,139 shares of common stock were reserved for future issuance under the Company's stock plans, including outstanding stock options, restricted stock units, and performance stock units that have been issued totaling 8,121,933 8,632,792 and 1,372,845 1,340,676 shares are available for future grants under the Company's 2017 Employee Stock Purchase Plan.

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

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

The exercise price of stock options granted under the Inducement Plan will not be less than the fair market value of a share of the Company's common stock on the grant date. Other terms of awards, including vesting requirements, are determined by the Company's board of directors and are subject to the provisions of the Inducement Plan. Stock options granted to employees generally vest over a four-year period but may be granted with different vesting terms. Certain options may provide for accelerated vesting in the event of a change in control. Stock options granted under the Inducement Plan expire no more than 10 years from the date of grant. As of September 30, 2022 March 31, 2023, 175,745 384,840 stock option awards have been issued under the Inducement Plan. As of September 30, 2022 March 31, 2023, 92,910 197,165 restricted stock unit awards have been granted under the Inducement Plan. As of September 30, 2022 March 31, 2023, 731,345 417,995 shares of common stock are available for future grant under the Inducement Plan.

On November 2, 2021, the Company entered into a sales agreement, or the Sales Agreement, with Cowen and Company LLC, or Cowen, as sales agent, pursuant to which the Company may, from time to time, issue and sell common stock with an aggregate value of up to $100,000 in "at-the-market" offerings, or the ATM. Sales of common stock, if any, pursuant to the Sales Agreement, may be made in sales deemed to be an "at the market offering" as defined in Rule 415(a) of the Securities Act, including sales made directly through The Nasdaq Global Market or on any other existing trading market for Company's common stock. As of September 30, 2022, there was $100,000 of common stock remaining available for sale under the ATM.

On February 9, 2021, the Company completed a public offering of 5,750,000 shares of common stock at an offering price of $30.00 per share, which included the exercise in full by the underwriters of their option to purchase up to 750,000 additional

shares of common stock. The Company received $161,731 in net proceeds after deducting underwriting discounts, commissions and offering expenses.

9. 11. Related-Party Transactions

Expenses paid directly to consultants and vendors considered to be related parties amounted to $467, $450, $1,445 $322 and $1,547 $480 for the three and nine months ended September 30, 2022 March 31, 2023 and 2021, 2022, respectively. Outstanding payments due to these related parties as of September 30, 2022 March 31, 2023 and December 31, 2021 December 31, 2022 were $42 $75 and $50, $13, respectively, and were included within accounts payable on the condensed consolidated balance sheet.

10. 12. Long-Term Obligations

On June 16, 2022, we entered into a RIFA with entities managed by HealthCare Royalty Management, LLC, collectively referred to as the Investors. Pursuant to the RIFA and subject to customary closing conditions, the Investors have agreed to pay the Company an aggregate investment amount of up to $100,000, or the Investment Amount. Under

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the terms of the RIFA, we received $37,500 on June 29, 2022 upon FDA approval of IMCIVREE in BBS, referred to as the Initial Investment Amount, and we received an additional $37,500 on September 29, 2022 of the Investment Amount upon EMA approval for BBS. We are entitled to receive the remaining $25,000 of the Investment Amount forty-five business days following achievement of a specified amount of cumulative net sales of IMCIVREE between July 1, 2022 and September 30, 2023.

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

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

the Investors may accelerate payments due under the RIFA up to the Hard Cap plus any other obligations payable under the RIFA.

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

We have evaluated the terms of the RIFA and concluded that the features are similar to those of a debt instrument. Accordingly, we have accounted for the transaction as long-term debt and presented it as a deferred royalty obligation on our condensed consolidated balance sheets. We have further evaluated the terms of the RIFA and determined that the repayment of the Hard Cap in effect at the time which ranges from 185% to 250% of the Investment Amount, less any payments made to date, upon a change of control is an embedded derivative that requires bifurcation from the debt instrument and fair value recognition. We determined the fair value of the derivative using an option pricing Monte Carlo simulation model taking into account the probability of change of control occurring and potential repayment amounts and timing of such payments that would result under various scenarios, as further described in Note 2, “Summary of Significant Accounting Policies” to our condensed consolidated financial statements. The aggregate fair value of the embedded derivative liability was $920 $1,290 and $1,340 as of September 30, 2022. March 31, 2023 and December 31, 2022, respectively. We will remeasure the embedded derivative to fair value each reporting period until the time the features lapse and/or termination of the deferred royalty obligation. For each of the three and nine month periods three-month period ended September 30, 2022 March 31, 2023 we recognized other income in the amount of $670, $50, due to the

remeasurement of the embedded derivative liability. The carrying value of the deferred royalty obligation at September 30, 2022 as of March 31, 2023 was $72,961 $77,520 based on $75,000 of proceeds, net of the fair value of the bifurcated embedded derivative liability upon execution of the RIFA, and debt issuance costs incurred. The carrying value of the deferred royalty

obligation approximated fair value at September 30, 2022 as of March 31, 2023 and was measured using Level 3 inputs. The estimated fair market value was calculated using an option pricing Monte Carlo simulation model with inputs consistent with those used in determining the embedded derivative values as described in Note 2, "Summary of Significant Accounting Policies." December 31, 2022. The effective interest rate as of September 30, 2022 March 31, 2023 was 17.28% 16.37%. In connection with the deferred royalty obligation, we incurred debt issuance costs totaling $2,662. Debt issuance costs have been netted against the debt and are being amortized over the estimated term of the debt using the effective interest method, adjusted on a prospective basis for changes in the underlying assumptions and inputs. The assumptions used in determining the expected repayment term of the debt and amortization period of the issuance costs requires that we make estimates that could impact the short and long-term classification of these costs, as well as the period over which these costs will be amortized.

11. Subsequent Events

On October 28, 2022, the Company delivered written notice, or the Notice, to RareStone that the Company has terminated the RareStone License for cause.

In accordance with the Notice, the Company maintains that RareStone has materially breached its obligations under the RareStone License to fund, perform or seek certain key clinical studies and waivers, including with respect to the Company's global EMANATE trial, among other obligations. RareStone has notified the Company that it objects to the claims in the Notice, including the Company's termination of the RareStone License for cause, and that a formal response is forthcoming.

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: the marketing and commercialization of IMCIVREE (setmelanotide), and the timing of commercialization; the success, cost and timing of our product development activities and clinical trials; our financial performance, including our expectations regarding

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our existing cash, operating losses, expenses and sources of future financing; our ability to hire and retain necessary personnel; patient enrollments and the timing thereof; the timing of announcements regarding results of clinical trials; our ability to protect our intellectual property; ongoing activities under and our ability to negotiate our collaboration and license agreements, if needed, and the impact of termination; our marketing, commercial sales, and revenue generation; expectations surrounding our manufacturing arrangements; the potential financial impact, growth prospects and benefits of our acquisition of Xinvento B.V.; the impact of the novel coronavirus, or COVID-19, pandemic and the current economic slowdown 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.

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Overview

We are a global, a commercial-stage biopharmaceutical company committed dedicated to transforming the lives of patients and their families living with rare diseases. We are focused on advancing our lead asset, IMCIVREE® (setmelanotide), as a precision medicine designed to treat hyperphagia and severe obesity caused by rare melanocortin 4 melanocortin-4 receptor (MC4R) pathway diseases. Rhythm's precision medicine, While obesity affects hundreds of millions of people worldwide, we are advancing IMCIVREE® (or setmelanotide), for a subset of individuals who have hyperphagia, a pathological hunger, and severe obesity due to an impaired MC4R pathway, which may be caused by traumatic injury or genetic variants. The MC4R pathway is an endocrine pathway in the brain that is responsible for regulating hunger, caloric intake and energy expenditure, which consequently affect body weight. IMCIVREE, an MC4R agonist for which we have exclusive hold worldwide rights, has the potential to restore dysfunctional MC4R pathway signaling and MC4R pathway function. MC4R pathway deficiencies result in the disruption of satiety signals and energy homeostasis in the body, which, in turn, leads to intense feelings of hunger and to obesity. IMCIVREE is the first-ever therapy developed for patients with hyperphagia and severe obesity caused by certain rare MC4R pathway ultra-rare diseases that is approved or authorized in the United States, European Union (EU) or and Great Britain. In the United States, IMCIVREE is approved by the U.S. Food and Drug Administration (FDA) for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndromic obesity due to pro-opiomelanocortin to: (i) proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency as determined by a U.S. Food and Drug Administration (FDA)-approved an FDA-approved test demonstrating variants in *POMC*,, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS); or (ii) Bardet-Biedl syndrome (BBS). The European Commission (EC) has and Great Britain's Medicines & Healthcare Products Regulatory Agency (MHRA) have authorized setmelanotide IMCIVREE for the treatment of obesity and the control of hunger associated with genetically confirmed BBS or genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. The UK's Medicines & Healthcare Products Regulatory Agency (MHRA) authorized setmelanotide for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. We have achieved market access for IMCIVREE for BBS or POMC and LEPR deficiencies, or both, in France, Germany and Great Britain, nine countries including the United States, and we expect continue to secure market collaborate with authorities to achieve and or expand access in Italy additional markets.

In addition to initial commercial efforts, we are advancing what we believe is the most comprehensive clinical research program ever initiated in MC4R pathway diseases, with multiple ongoing and planned Phase 2 and Phase 3 clinical trials evaluating setmelanotide.

We are developing setmelanotide to address additional patients with acquired hypothalamic obesity. In our Phase 2 trial evaluating setmelanotide as a treatment for hypothalamic obesity, as announced in November 2022, 16 of 18 patients achieved the Netherlands primary endpoint with a body mass index (BMI) decrease greater than 5 percent on setmelanotide therapy, and we observed a 14.5 mean percent reduction in BMI across all patients. On May 2, 2023, we announced that the first patients were dosed in our pivotal Phase 3 trial evaluating setmelanotide in patients with acquired hypothalamic obesity. The Phase 3 clinical trial is designed to enroll 120 patients aged 4 years or older randomized 2:1 to setmelanotide therapy or placebo for a total of 60 weeks, including up to eight weeks for dose titration. The primary endpoint is the percent change in BMI after approximately 52 weeks on a therapeutic regimen of setmelanotide versus placebo. Key secondary

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endpoints include the proportion of patients who achieve ≥5% reduction in BMI from baseline in adults (≥18) or BMI Z-score reduction of ≥0.2 from baseline in pediatrics after approximately 52 weeks on a therapeutic regimen of compared with placebo, and mean change in the fourth weekly average of the daily most hunger score in patients ≥12 years from baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide versus placebo. We anticipate completing enrollment in this trial in the first quarter of 2022.2024.

In addition, our ongoing pivotal Phase 3 EMANATE and Phase 2 DAYBREAK trials are designed to United States, EU and UK, we and our partners are seeking approval and market access for IMCIVREE to treat patients with these evaluate setmelanotide in several distinct, genetically defined MC4R pathway-related obesities in Argentina and Israel.

pathway diseases. We also are advancing conducting a broad clinical development program Phase 3 pediatrics trial evaluating daily setmelanotide in several ongoing clinical trials, patients between the ages of two and we six and a Phase 3 switch trial evaluating a weekly formulation of setmelanotide.

We are leveraging what we believe is the largest known DNA database focused on obesity - with approximately 45,000 60,000 sequencing samples as of December 31, 2021 December 31, 2022 - to improve the understanding, diagnosis and care of people living with severe obesity due to certain variants in genes associated with the MC4R pathway. In April 2022, we enrolled the first patient Our sequencing-based epidemiology estimates show that each of these genetically defined MC4R pathway deficiencies number in the pivotal Phase 3 EMANATE clinical trial, a randomized, double-blind, placebo-controlled trial rare or ultra-rare category, according to evaluate setmelanotide established definitions of rare disease patient populations. Our epidemiology estimates are approximately 4,600 to 7,500 for U.S. patients in four independent sub-studies in patients with initial FDA-approved indications, including obesity due to a heterozygous variant of the *POMC/ biallelic POMC, PCSK1* genes or *LEPR* gene or certain rare variants of the SRC1 gene or the SH2B1 gene. We also have initiated the Phase 2 DAYBREAK clinical trial designed to evaluate setmelanotide in patients who carry a confirmed variant in one or more of 10 additional genes with strong or very strong relevance to the MC4R pathway. In November 2022, we announced plans to initiate a pivotal, Phase 3 trial to evaluate setmelanotide in deficiencies, and BBS. Epidemiology estimates for patients with hypothalamic obesity is between 5,000 and 10,000 in early 2023. In addition, the United States, based on our broad clinical programs evaluating setmelanotide analysis of published literature and our epidemiology estimates for the indications being studied in rare MC4R pathway diseases include the ongoing our Phase 3 study in pediatric EMANATE trial suggest that approximately 53,000 U.S. patients with MC4R pathway deficiencies between one of these genetically driven obesities have the ages of 2 and 6 years old, and a potential registration-enabling study with our once-weekly formulation of to respond well to setmelanotide. Additionally,

as an FDA post-marketing requirement, we are currently evaluating the effects of setmelanotide on the QT interval corrected for heart rate, or QTc interval, in healthy volunteers.

There are currently no effective or approved treatments for these rare MC4R pathway related diseases. The FDA has acknowledged the importance of these results by giving setmelanotide Breakthrough Therapy designation for the treatment of obesity associated with genetic defects upstream of the MC4R in the leptin melanocortin pathways. The Breakthrough Therapy designation currently covers indications for POMC deficiency obesity, LEPR deficiency obesity, BBS and, as of November 2022, hypothalamic obesity.

Additional recent clinical, regulatory and commercial updates include:

On November 8, 2022 February 27, 2023, we completed the acquisition of Xinvento B.V. (Xinvento), a Netherlands-based biotech company focused on developing therapies for congenital hyperinsulinism (CHI). At closing, Rhythm BV, pursuant to a Share Purchase Agreement, or the Purchase Agreement, with Xinvento, acquired all of the issued and outstanding shares of Xinvento for aggregate consideration of $5 million, as adjusted pursuant to the terms of the Purchase Agreement and subject to the distribution and payment terms set forth therein. In addition, the Purchase Agreement provides for the payment of additional consideration totaling up to $206.0 million upon achievement of certain development, regulatory and commercial milestones by Xinvento. CHI is a rare genetic disease in which cells secrete excess insulin, causing hypoglycemia, which can result in serious health outcomes including seizures, coma, permanent brain damage and death. We plan to expand our pipeline into CHI, a rare disease that is well aligned with our corporate strategy and our focus on rare endocrinology indications.

On May 2, 2023, we announced that as of September 30, 2022, we had received more than 80 physicians have written more than 120 300 new prescriptions for IMCIVREE for patients BBS from more than 175 physicians in the United States with BBS since IMCIVREE was approved by the FDA. We have secured approval for reimbursement approvals for more than 40 160 of those prescriptions. prescriptions from FDA approval between June 16, 2022 to March 31, 2023. More than 100 of the total new prescriptions were written in the first quarter of 2023.

On November 2, 2022 April 24, 2023, we also announced the design commercial launch of our Phase 3 clinical trial IMCIVREE in acquired hypothalamic Germany for the treatment of obesity following recent discussions and control of hunger associated with BBS with federal reimbursement. The German Federal Joint Committee (G-BA) previously ruled that IMCIVREE is eligible for reimbursement by Statutory Health Insurances for BBS based on its unanimous vote to exclude IMCIVREE from its lifestyle exemption list for patients with BBS.

On March 27, 2023, we announced the FDA. The trial, which is anticipated to initiate publication of research in early 2023, is expected to enroll the peer-reviewed journal *Advances in Therapy* that demonstrated setmelanotide improved hyperphagia and reduced obsessive focus on food and body weight in patients

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120 patients randomized 2:1 to setmelanotide therapy or placebo for 60 weeks, including up to 8 weeks for dose titration. The primary endpoint will be the percent change in body mass index (BMI) versus placebo. Key secondary endpoints will include the proportion of patients who achieve ≥5% reduction in BMI from baseline in adults (≥18) or BMI Z-score reduction of ≥0.2 from baseline in pediatrics at Week 60 compared with placebo; and mean change in the weekly average of the daily most hunger score in patients ≥12 years from baseline to Week 60 compared with placebo.

At The Obesity Society's ObesityWeek® 2022 conference held November 1-4, 2022 in San Diego, California, we and our collaborators delivered 11 presentations. Highlights from the presentations include:

- Positive full dataset from our Phase 2 trial evaluating setmelanotide for the treatment of hypothalamic obesity demonstrating that 89% percent (16 of 18) patients had a 5% or greater reduction in BMI at 16 weeks; 14.5 mean percent reduction in BMI and 12.6 mean percent reduction body weight (N=18) at Week 16 from baseline;

- Additionally, we reported that 14 patients continued on therapy in our long-term extension trial. As of a cut-off date of September 23, 2022, 13 of these patients who reached a total of 29 weeks on setmelanotide therapy achieved a mean BMI reduction of 21.1% (SD, 11.2%); and five (5) of these patients who reached a total of 41 weeks on setmelanotide therapy achieved a mean BMI reduction of 26.7% (SD, 12.4%).

- Results from the Clinical Registry Investigating Bardet-Biedl Syndrome (CRIBBS): We also presented results from CRIBBS, the international registry of patients with BBS that launched in 2014. We collaborated with the Marshfield Clinic Research Institute on multiple analyses of blinded CRIBBS data. The results demonstrated that children with BBS experience high disease burden due to hyperphagia and that hyperphagia was positively correlated with higher BMI weight categories. Obesity was found to be highly prevalent in a large sample of children with BBS and most children who had obesity continued to have it or experienced worsening weight gain over time.

On November 1, 2022, we also announced that the FDA has granted Breakthrough Therapy designation to setmelanotide for the treatment of hypothalamic obesity. The FDA's Breakthrough Therapy designation is designed to expedite development and review of medicines that aim to address a serious condition with preliminary clinical evidence indicating that the drug may demonstrate substantial improvement over existing treatments on one or more clinically significant endpoints.

On October 12, 2022, we announced our sponsorship of the inaugural International Meeting on Pathway-Related Obesity: Vision of Excellence (IMPROVE) 2022 in Berlin, Germany, bringing together approximately 100 specialists to share the latest scientific developments and patient care practices related to rare MC4R pathway-related obesities.

Also on October 12, 2022 at IMPROVE, we announced data from our exploratory Phase 2 Basket Study evaluating setmelanotide in patients stratified into two cohorts, one with predicted setmelanotide rescuable MC4R pathway deficiency and one with predicted nonrescuable MC4R deficiency.

On October 6, 2022, we announced the appointment of Dana Washburn, M.D., as Senior Vice President of Clinical Development and as a member of our Executive Leadership Team to lead our robust clinical development program, clinical operations, and data management.

On September 23, 2022, we announced the publication of a children's book developed in collaboration with the BBS Foundation entitled, "Understanding Hunger & Bardet-Biedl Syndrome (BBS): Gabe's Story."

On September 19, 2022, we completed a public offering of 4,800,000 shares of common stock at a price to the public of $26.00 per share for aggregate net proceeds to us of $117.0 million, after deducting underwriting discounts and commissions and offering expenses payable by us. On October 18, 2022, we completed the sale of an additional 580,000 shares of common stock at a price to the public of $26.00 per share pursuant to the partial exercise assessment of the underwriters'

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option to purchase additional shares, for aggregate net proceeds to us severe hyperphagia on patients' quality of approximately $131.2 million, after deducting underwriting discounts, commissions and offering expenses payable by us.

On September 19, 2022, we announced presentations during the 60th Annual Meeting of the European Society for Paediatric Endocrinology (ESPE 2022) held in Rome, Italy that detailed new findings on the burden of hyperphagia and obesity on patients with BBS and their caregivers and data from new analyses that showed setmelanotide achieved substantial weight loss benefit in adolescent and pediatric patients with rare MC4R pathway diseases across three separate pivotal trials.

On September 6, 2022, we announced that the EC has expanded the marketing authorization for IMCIVREE to include the treatment of obesity and control of hunger associated with genetically confirmed BBS in adult and pediatric patients 6 years of age and older.

Also on September 6, 2022, we announced that Health Canada granted Priority Review for our New Drug Submission (NDS) for setmelanotide, indicated in adult and pediatric patients 6 years of age and older with impairments life in the MC4R pathway due to genetic diseases, for the treatment of obesity open-access journal *Obesity Science and control of hunger in BBS or biallelic POMC, PCSK1, LEPR deficiency. Priority Review shortens Health Canada's submission review performance target to 180 days, in comparison to 300 days for non-Priority Review. Practice*.

In addition, we reported that we We also expect to achieve the following near-term milestones:

- Launch Present data analyses from the Phase 2 and long-term extension trials in hypothalamic obesity in the fall of 2023;
- Complete regulatory review by Health Canada and, pending approval, make IMCIVREE commercially available in Italy and Canada for the Netherlands for patients with treatment of BBS, or POMC, PCSK1 or LEPR deficiencies in the fourth quarter second half of 2022;
- Initiate pivotal Phase 3 trial to evaluate setmelanotide in hypothalamic obesity in early 2023;
- Initiate a Phase 3, randomized, double-blind trial in patients naïve to setmelanotide therapy ("de novo study") to evaluate the weekly formulation of setmelanotide in patients with BBS in the first second half of 2023;
- Complete regulatory review by Health Canada and, pending approval, make IMCIVREE commercially available Announce preliminary data from the open-label part of the Phase 2 DAYBREAK trial from one or more genetically defined cohorts in Canada for the treatment second half of obesity and control of hunger in adults and pediatric patients 6 years and older with BBS, or with POMC, PCSK1 or LEPR deficiencies in 2023; and
- Announce topline data from our the ongoing Phase 3, open-label pediatrics trial evaluating one year of setmelanotide therapy in pediatric patients with MC4R pathway deficiencies between the ages of 2 two and 6 six years old in the second half of 2023. 2023;
- Announce topline data from the ongoing Phase 3 switch trial evaluating a weekly formulation of setmelanotide in the second half of 2023; and
- Provide an update on early-stage R&D efforts in the fourth quarter of 2023, including details of the CHI pre-clinical development program and IND expected in 2024.

Our operations to date have been limited primarily to conducting research and development activities for setmelanotide. To date, we have not generated less than $15.0 million of revenue sufficient cash flows from product sales and we have financed our operations primarily through the proceeds received from the sales of common and preferred stock, royalty interest financing, asset sales, collaboration and license agreements, as well as capital contributions from the former parent company, Rhythm Holdings LLC. From August 2015 through August 2017, we raised aggregate net proceeds of $80.8 million through our issuance of series A preferred stock. Since our initial public offering, or IPO, on October 10, 2017 and our underwritten follow-on offerings through October 2022, we have raised aggregate net proceeds of approximately $742.6 million through the issuance of our common stock after deducting underwriting discounts, commissions and offering related transaction costs. We also received $100.0 million from an asset sale, specifically in connection with the sale of our PRV. Rare Pediatric Disease Priority Review Voucher,or PRV, to Alexion Pharmaceuticals, Inc. in February 2021. In December 2021, we

entered into an Exclusive License Agreement with RareStone Group Ltd., and received $7.0 million in connection with the execution of that agreement. In June 2022, we entered into the Revenue Interest Financing Agreement, or RIFA, (as defined below) with entities managed by HealthCare Royalty Partners, LLC, or HealthCare Royalty, and received cumulative proceeds of $74.8 million $73.2 million, net of certain transaction costs at closing. Additionally, there is $25.0 million of additional proceeds available to us under our RIFA if certain sales-based milestones are achieved during 2023.

We will not generate significant revenue from product sales until we are able to successfully establish a marketing and commercialization infrastructure for IMCIVREE.

IMCIVREE became commercially available to patients 6 years of

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age and older with obesity due to POMC, PCSK1 or LEPR deficiency in the U.S. in the first quarter of 2021 and patients 6 years of age and older with obesity due to BBS during June 2022. Following marketing authorizations in the EU and Great Britain, we are pursuing a country-by-country strategy to establish market access and reimbursement for IMCIVREE in several countries. During March 2022, we treated the first patients with IMCIVREE in France under the paid early access program and we treated the first patients with IMCIVREE in Germany during June 2022. We expect to continue to fund our operations through the sale of equity, debt financings or other sources. We intend to build have built our own marketing and commercial sales infrastructure in the United States

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and we are in the process of building a similar infrastructure in several European markets and the United Kingdom. We may enter into collaborations with other parties for certain markets outside the United States. However, we may be unable to raise additional funds or enter into such other arrangements when needed on favorable terms, or at all. If we fail to raise capital or enter into such other arrangements as, and when, needed, we may have to significantly delay, scale back or discontinue the development or commercialization of setmelanotide.

As of September 30, 2022, March 31, 2023 we had an accumulated deficit of $667.6 $762.2 million. Our net losses were $40.9 million, $35.1 million, $138.6 million, $52.2 million and $26.7 million $52.8 million, for the three and nine months ended September 30, 2022 March 31, 2023 and 2021, 2022, respectively. We expect to continue to incur significant expenses and increasing operating losses over the foreseeable future. We expect our expenses will increase substantially in connection with our ongoing activities, as we:

- continue to conduct clinical trials for setmelanotide;
- engage contract manufacturing organizations, or CMOs, for the manufacture of clinical and commercial-grade setmelanotide;

- seek regulatory approval for setmelanotide for additional indications;
- expand our clinical, regulatory, commercial and corporate infrastructure and expand operations globally;
- engage in the sales and marketing efforts necessary to support the continued commercial efforts of IMCIVREE globally;
- take into account the levels, timing and collection of revenue earned from sales of IMCIVREE and other products approved in the future, if any; and
- continue to operate as a public company.

As of September 30, 2022 March 31, 2023, our existing cash and cash equivalents and short-term investments were approximately $347.8 $294.6 million. We expect that our previously announced changes to the EMANATE and DAYBREAK trials, coupled with a streamlining of our planned global network of clinical trial sites, will result in meaningful cost savings. We expect that our existing cash and cash equivalents and short-term investments will be sufficient to fund our operations into 2025.

Corporate Background

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

Impact of COVID-19

We are closely monitoring how the continued spread of COVID-19 is affecting our employees, business, preclinical studies and clinical trials. In response to the COVID-19 pandemic, we have limited access to our executive offices with most employees continuing their work outside of our offices and travel has been restricted. Based on current information we do not currently anticipate any disruption in the clinical supply of setmelanotide. Our CMOs have indicated that they have appropriate plans and procedures in place to ensure uninterrupted future supply of clinical and commercial-grade setmelanotide, subject to potential limitations on their operations due to COVID-19. As a result, we do not currently expect that the COVID-19 pandemic will have a material impact on our business, results of operations and financial condition. At this time, however, there is still uncertainty relating to the trajectory of the pandemic and the impact of

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related responses, and disruptions caused by the COVID-19 pandemic have resulted and may in the future result in difficulties or delays in initiating, enrolling, conducting or completing our planned and ongoing clinical trials and the incurrence of unforeseen costs as a result of disruptions in clinical supply or preclinical study or clinical trial delays. For example, in 2020, we experienced interruption of key clinical trial activities, such as patient attendance and clinical trial site monitoring, in our Phase 3 clinical trial evaluating setmelanotide for the treatment of insatiable hunger and severe obesity in individuals with BBS or Alström syndrome. The impact of COVID-19 on our future results will largely depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as the duration of the pandemic, the impact of variants, evolving travel restrictions and social distancing in the United States and other countries, business closures or business disruptions, the ultimate impact on financial markets and the global economy, the effectiveness of vaccines and vaccine distribution efforts and the effectiveness of other actions taken in the United States and other countries to contain and treat the disease. See "Risk Factors—The COVID-19 pandemic has and may continue to adversely impact our business, including our preclinical studies, clinical trials and our commercialization prospects." in Part II, Item 1A of this Quarterly Report on Form 10-Q.

Financial Operations Overview

Revenue

To date, we have generated less than $15.0 million $35.0 million of revenue from product sales. Our lead product candidate, IMCIVREE, was approved by the FDA in November 2020 for chronic weight management in adult and pediatric patients six years of age and older with obesity due to POMC, PCSK1 or LEPR deficiency confirmed by genetic testing. IMCIVREE became commercially available in the United States in the first quarter of 2021. We recorded our first sales of IMCIVREE in the United States in March 2021 and we made our first sales in France during March 2022 under the paid early access program. IMCIVREE was approval by the FDA and the EC in adult and pediatric patients six years of age and older with obesity due to BBS in June and September of 2022, respectively. Following these approvals for BBS, we expect our sales of IMCIVREE will continue to grow as we identify and treat more patients with this disease and obtain reimbursement throughout the international markets in which we operate.

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Cost of sales

All of our inventory of IMCIVREE produced prior to FDA approval is available for commercial or clinical use. Most of the manufacturing costs have been recorded as research and development expenses in prior periods. Accordingly, the costs for product cost component related to IMCIVREE included in our cost of sales for the three and nine months ended September 30, 2022 were March 31, 2023 and 2022 was insignificant. We expect cost of sales to increase in 2022 2023 as we continue to sell inventory that is produced after we began capitalizing manufacturing costs for IMCIVREE commercial inventory. We continue to evaluate the impact of this previously expensed inventory on the future cost of product sales, however we do not expect there to be a significant impact to our cost of sales based on the cost structure of the product.

Research and development expenses

Research and development expenses consist primarily of costs incurred for our research activities, including our drug discovery and genetic sequencing efforts, and the clinical development of setmelanotide, which include:

- expenses incurred under agreements with third parties, including CROs that conduct research and development and preclinical activities on our behalf, and the cost of consultants and CMOs that manufacture drug products for use in our preclinical studies and clinical trials;
- employee-related expenses including salaries, benefits and stock-based compensation expense;
- the cost of lab supplies and acquiring, developing and manufacturing preclinical and clinical study materials;
- the cost of genetic sequencing of potential patients in clinical studies; and

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- 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:

	Three Months Ended September 30,		Nine Months Ended September 30,		Three Months Ended March 31,	
Research and development summary	**2022**	**2021**	**2022**	**2021**	**2023**	**2022**
Research and development expense	$ 21,116	$ 27,539	$ 85,082	$ 72,554	$37,945	$32,510

We are unable to predict the duration and costs of the current or future clinical trials of our product candidates. The duration, costs, and timing of clinical trials and development of setmelanotide will depend on a variety of factors, including:

- the scope, rate of progress, and expense of our ongoing, as well as any additional, clinical trials and other research and development activities;
- the rate of enrollment in clinical trials;
- the safety and efficacy demonstrated by setmelanotide in future clinical trials;
- changes in regulatory requirements;
- changes in clinical trial design; and

- the timing and receipt of any regulatory approvals.

A change in the outcome of any of these variables with respect to the development of our product candidates would significantly change the costs and timing associated with its development and potential commercialization.

Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect research and development costs to increase significantly for the foreseeable future as our setmelanotide and other development programs progress. However, we do not believe that it is possible at this time to accurately project total program-specific expenses to commercialization and there can be no guarantee that we can meet the funding needs associated with these expenses.

Selling, general and administrative expenses

Selling expenses consist of professional fees related to preparation for the commercialization of setmelanotide, as well as salaries and related benefits for commercial employees, including stock-based compensation. As we further implement and execute our commercialization plans and start to market setmelanotide in new territories and as we explore new collaborations to develop and commercialize setmelanotide, we anticipate that these expenses will materially increase.

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

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

	Three Months Ended September 30,		Nine Months Ended September 30,		Three Months Ended March 31,	
Selling, general and administrative summary	**2022**	**2021**	**2022**	**2021**	**2023**	**2022**
Selling, general and administrative expense	$ 21,938	$ 17,507	$ 65,715	$ 47,490	$24,634	$21,449

We anticipate that our selling, general and administrative expenses will increase in the future to support continued and expanding development commercialization efforts commercialization of for IMCIVREE in the United States and the European Union as well as increased costs of operating as a global commercial stage biopharmaceutical public company. These increases will likely include increased costs related to the hiring of additional personnel and fees to outside consultants, lawyers and accountants, compliance with local rules and regulations in the United States and foreign jurisdictions, exchange listing and Securities and Exchange Commission (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.

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, 2021 December 31, 2022.

Results of Operations

Comparison of the three months ended September 30, 2022 March 31, 2023 and 2021 2022

The following table summarizes our results of operations for the three months ended September 30, 2022 March 31, 2023 and 2021, 2022, together with the changes in those items in dollars and as a percentage:

	Three Months Ended September 30,		Change		Three Months Ended March 31,		Change	
	2022	2021	$	%	2023	2022	$	%
	(in thousands)				(in thousands)			
Statement of Operations Data:								
Product revenue, net	$ 4,284	$ 1,028	$ 3,256	317 %	$ 11,469	$ 1,498	$9,971	666 %
Costs and expenses:								
Cost of sales	497	222	275	124 %	1,421	230	1,191	518 %
Research and development	21,116	27,539	(6,423)	(23)%	37,945	32,510	5,435	17 %
Selling, general, and administrative	21,938	17,507	4,431	25 %	24,634	21,449	3,185	15 %
Total costs and expenses	43,551	45,268	(1,717)	(4)%	64,000	54,189	9,811	18 %
Loss from operations	(39,267)	(44,240)	4,973	(11)%	(52,531)	(52,691)	160	(0)%
Other (expense) income, net	(1,594)	138	(1,732)	(1,255)%				
Loss before taxes	(40,861)	(44,102)	3,241	(7)%				
Benefit from income taxes	—	(8,995)	8,995	(100)%				
Other income (expense), net					352	(73)	425	(582)%
Net loss	$ (40,861)	$ (35,107)	$ (5,754)	16 %	$(52,179)	$(52,764)	$ 585	(1)%

NM=Not meaningful

Product revenue, net. Product revenue, net increased by $3.3 $10.0 million to $4.3 $11.5 million for the three months ended September 30, 2022 March 31, 2023 from $1.0 $1.5 million for the three months ended September 30, 2021 March 31, 2022, an increase of 317% 666%. The FDA approved our lead product candidate, IMCIVREE in November 2020 During the three months ended March 31, 2023 and we recorded our first sales of IMCIVREE in March 2021. We expect our sales of IMCIVREE to continue to increase following the FDA approval for the treatment of patients with BBS in the United States during June 2022, and by the EC in September 2022. Through September 30, 2022, a substantial amount of our product revenue, or 81% 83% and 98%, respectively, has been generated in the United States. During March 2022, we completed our first sales of IMCIVREE in France through an early access program. During June 2022, we completed our first sales of IMCIVREE in Germany.

Cost of sales. Cost of sales increased by $0.3 million $1.2 million to $0.5 million $1.4 million for the three months ended September 30, 2022 from $0.2 million for the three month period ended September 30, 2021. All March 31, 2023, an increase of our inventory of IMCIVREE produced prior to FDA approval is available for commercial or clinical use. 518%. Most of the IMCIVREE manufacturing costs have been recorded as research and development expenses in prior periods. Accordingly, the costs for product cost component related to IMCIVREE included in our cost of sales for the three months ended September 30, 2022 March 31, 2023 and 2021 were insignificant 2022 was insignificant. Cost of sales primarily reflects a royalty due to Ipsen Pharma S.A.S., or Ipsen, on our net product sales and primarily reflect the amortization of our capitalized sales based sales-based milestone payment made to Ipsen Pharma S.A.S., or Ipsen, upon our first commercial sale in the United States U.S. and European Union, as well as a royalty EU. Specifically, the $1.2 million increase in cost of sales for the three months ended March 31, 2023 was due to Ipsen on $0.5 million of additional royalties due to our net growth in sales, $0.6 million attributed to product sales. cost primarily associated with higher sales volume and product distributed for our patient assistance program, and $0.1 million of additional amortization. We expect cost of sales to increase over time as we sell inventory that is produced after we began capitalizing IMCIVREE commercial inventory.

Research and development expense. Research and development expense decreased increased by $6.4 $5.4 million to $21.1 $37.9 million in 2023 from $32.5 million in 2022, from $27.5 million in 2021, a decrease an increase of 23% 17%. The decrease net increase was primarily due to the following:

- the purchase of in-process research and development assets of $5.4 million from Xinvento;
- an increase of $2.6 million in salaries, benefits and stock-based compensation related to the hiring of additional full-time employees in order to support the growth of our research and development programs; and
- an increase of $1.7 million due to increased gene sequencing costs to support our expanded clinical programs.

The above increases were partially offset by:

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- a decrease of $5.2 million $2.8 million in our clinical trial costs associated with the impact of study design amendments to our Phase 2 DAYBREAK study, as well as, reduced activity due to the completion and winding down of our Phase 2 hypothalamic obesity study, Phase 2 DAYBREAK, QTc trial, BBS QT, trial, Phase 2 Basket trial, Phase 3 pediatrics trial and our renal studies; these study, long-term extension and switch trials. These decreases were partially offset by increased costs associated with activity in our Phase 3 EMANATE trials, and increased enrollment in our long-term extension Phase 3 hypothalamic obesity study;
- a decrease of $1.3 million $0.7 million in costs associated with the manufacturing of clinical material;
- a decrease of $0.5 million of costs related to next generation research and development activities;
- a decrease of $0.4 million in costs associated with medical affairs; and
- a decrease of $0.3 million $1.0 million in compensation and benefits.

The above decreases were partially offset by:

- an increase of $1.2 million due development milestones earned by Camurus AB, or Camurus related to increased gene sequencing costs development milestone achieved related to support our expanded clinical programs. weekly formulation.

Selling, general and administrative expense. Selling, general and administrative expense increased by $4.4 million $3.2 million to $21.9 million $24.6 million in 2022 2023 from $17.5 million $21.4 million in 2021, 2022, an increase of 25% 15%. The increase was primarily due to the following:

- an increase of $2.2 million $2.6 million due to increased compensation and benefits related costs associated with additional headcount to support our expanding business operations as well as to build out our commercial operations in the United States and internationally;

- an increase of $1.6 million due to increased costs associated with insurance premiums, office support, travel and entertainment related costs for our expanding workforce and increased commercial operations; and

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- an increase of $0.7 million related to increased costs associated with sales and marketing activities for IMCIVREE in connection with preparing for the EC approval for BBS obtained in September 2022 and expanding our international market access.

The above increases were partially offset by:

- a decrease of $0.4 million $1.0 million related to professional services costs.

Other (expense) income, net. Other (expense) income, net decreased by $1.7 million to ($1.6) million for the three months ended September 30, 2022. Other (expense) income, net consists of ($2.1) million of interest expense related to our RIFA with HealthCare Royalty Partners, LLC and a ($1.0) million write off expense related to our RareStone equity partially offset by $1.0 million of interest income primarily due to improving interest rates during the period and $0.7 million fair market value adjustment related to our RIFA embedded derivative.

(Benefit from) provision for income taxes. There is no provision for income taxes for the three months ended September 30, 2022, as we project to generate operating losses during the year. We recorded an income tax benefit of $9.0 million as a result of the reversal of a tax provision recorded upon the sale of our PRV during the three months ended September 30, 2021.

Net loss. Net loss increased by $5.8 million to $40.9 million for the three months ended September 30, 2022, from net loss of $35.1 million for the three months ended September 30, 2021. The increase in net loss was a result of higher costs as noted above, offset by current period revenues, and the non-recurring nature of the impact of a tax benefit related to the sale of our PRV in the prior year period.

Comparison of the nine months ended September 30, 2022 and 2021

The following table summarizes our results of operations for the nine months ended September 30, 2022 and 2021, together with the changes in those items in dollars and as a percentage:

	Nine Months Ended September 30,	Change

	2022	2021	$	%
	(in thousands)			
Statement of Operations Data:				
Product Revenue, net	$ 8,094	$ 1,337	$ 6,757	505 %
License revenue	6,754	—	6,754	NM
Costs and expenses:				
Cost of sales	1,105	363	742	204 %
Research and development	85,082	72,554	12,528	17 %
Selling, general, and administrative	65,715	47,490	18,225	38 %
Total costs and expenses	151,902	120,407	31,495	26 %
Loss from operations	(137,054)	(119,070)	(17,984)	15 %
Other (expense) income, net	(1,572)	100,313	(101,885)	(102)%
Loss before taxes	(138,626)	(18,757)	(119,869)	639 %
Provision for income taxes	—	7,989	(7,989)	(100)%
Net loss	$ (138,626)	$ (26,746)	$ (111,880)	418 %

NM=Not meaningful

Product revenue, net. Product revenue, net increased by $6.8 million to $8.1 million for the nine months ended September 30, 2022 from $1.3 million for the nine months ended September 30, 2021, an increase of 505%. The FDA approved our lead product candidate, IMCIVREE in November 2020 and we recorded our first sales of IMCIVREE in March 2021. We expect our sales of IMCIVREE to continue to increase following the FDA approval for the treatment of

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patients with BBS in the United States during June 2022 and by the EC during September 2022. Through September 30, 2022, substantially all of our product revenue, or 86%, has been generated in the United States. During March 2022, we completed our first sales of IMCIVREE in France through an early access program. During June 2022, we completed our first sales of IMCIVREE in Germany.

License revenue. License revenue was $6.8 million for the nine months ended September 30, 2022 and was entirely related to the RareStone license. We entered into a license agreement with the RareStone in December 2021 and completed our activities required to transfer the license to RareStone during the second quarter of 2022, which resulted in the recognition of the license revenue. We do not expect to recognize additional license revenue related to the RareStone arrangement during 2022.

Cost of sales. Cost of sales increased by $0.7 million to $1.1 million for the nine months ended September 30, 2022 from $0.4 million in the nine months ended September 30, 2021, an increase of 204%. Most of the IMCIVREE manufacturing costs have been recorded as research and development expenses in prior periods. Accordingly, the product cost component related for IMCIVREE included in our cost of sales for the nine months ended September 30, 2022 were insignificant and cost of sales primarily reflect the amortization of our capitalized sales based milestone payment made to Ipsen Pharma S.A.S., or Ipsen, upon our first commercial sale in the United States and European Union, as well as a royalty due to Ipsen on our net product sales. The $0.7 million increase in cost of sales was due to an increase of $0.3 million of additional amortization, $0.3 million of additional royalties due to our growth in sales and $0.1 attributed to product cost primarily associated with higher sales

volume. We expect cost of sales to increase overtime as we sell inventory that is produced after we began capitalizing IMCIVREE commercial inventory.

Research and development expense. Research and development expense increased by $12.5 million to $85.1 million in the nine months ended September 30, 2022 from $72.6 million in the nine months ended September 30, 2021, an increase of 17%. The increase was primarily due to the following:

- an increase of $8.8 million in our clinical trial costs associated with new and planned clinical trials, including our Phase 2 DAYBREAK and Phase 3 EMANATE trials, Phase 3 pediatrics trial, QTc study, Phase 2 hypothalamic obesity study, and increased enrollment in our long-term extension study. These increases were partially offset by reduced activity due to the completion and winding down of our POMC LEPR, BBS, Phase 2 Basket, renal and GO-ID studies;
- an increase of $3.0 million due to increased purchases of clinical supply material;
- an increase of $2.4 million due to increased gene sequencing costs associated with our expanded clinical programs;
- an increase of $1.1 million in compensation and benefits due to the hiring of additional full-time employees in order to support the growth of our research and development programs and expansion of regulatory affairs operations;
- an increase of $1.0 million in development milestones earned by Camurus AB, or Camurus, related to development milestone achieved related to our weekly formulation; costs; and
- an increase of $0.3 million related to IP and patent related filing activities.

The above increases were partially offset by:

- a decrease of $3.7 million in costs associated with medical affairs; and
- a decrease of $0.7 million in costs associated with next generation research and development activities.

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Selling, general and administrative expense. Selling, general and administrative expense increased by $18.2 million to $65.7 million in the nine months ended September 30, 2022 from $47.5 million in the nine months ended September 30, 2021, an increase of 38%. The increase was primarily due to the following:

- an increase of $8.1 million related to increased costs associated with commercial operations, sales and marketing activities for IMCIVREE in connection with preparing for the U.S. approval for BBS obtained in June 2022 and EC approval in September 2022;
- an increase of $6.6 million due to increased compensation and benefits related costs associated with additional headcount to support our expanding business operations as well as to build out our commercial operations in the United States and internationally; and
- an increase of $3.6 million $0.9 million due to increased costs associated with information technology, international office space, sponsorships and general corporate travel related expenses for our expanding workforce. workforce

The above increases were partially offset by:

- a decrease of $1.2 million related to costs associated with sales and marketing activities for IMCIVREE in preparation of BBS launch during the prior year.

Other income (expense) income, , net. Other (expense) income (expense), net decreased increased by $101.9 million $0.4 million to ($1.6) million in $0.4 million for the nine three months ended September 30, 2022 March 31, 2023. The decrease was Total other income (expense), net for the three months ended March 31, 2023 consists of interest income of $3.4 million primarily due to the sale of our PRV in February 2021. The sale of our PRV in the prior year was a non-recurring transaction. Other (expense) income, net consists of $2.2 million improved interest rates, partially offset by $3.0 million of interest expense related to our RIFA with HealthCare Royalty and a $1.0 million write-off expense $0.1 million fair market value adjustment related to our RareStone equity RIFA embedded derivative.

Net loss. Net loss decreased by $0.6 million to $52.2 million for the nine three months ended September 30, 2022 March 31, 2023, partially offset by $1.4 million of interest income and $0.7 million of other income resulting from the remeasurement of our embedded derivative related to our RIFA.

Provision for income taxes. There is no provision for income taxes for the nine months ended September 30, 2022, as we project to generate operating losses during the year. We recorded a provision for income taxes of $8.0 million as a result of the sale of our PRV during the nine months ended September 30, 2021.

Net loss. Net loss increased by $111.9 million to $138.6 million for the nine months ended September 30, 2022, from net loss of $26.7 million $52.8 million for the nine three months ended September 30, 2021 March 31, 2022. The increase decrease in net loss was primarily a result of the non-recurring nature of our PRV sale in 2021, which resulted in $100.0 million of

higher product revenue, net and other income during the prior year period, as well as higher costs partially (expense), net, offset by product higher current period costs and license revenue in the current year expenses, as noted above.

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Liquidity and Capital Resources

As of September 30, 2022 March 31, 2023, our cash and cash equivalents and short-term investments were approximately $347.8 $294.6 million.

Cash flows

The following table provides information regarding our cash flows for the nine three months ended September 30, 2022 March 31, 2023 and 2021: 2022:

	Nine Months Ended September 30,		Three Months Ended March 31,	
	2022	2021	2023	2022
	(in thousands)		(in thousands)	
Net cash provided by (used in):				
Net cash (used in) provided by:				
Operating activities	$ (139,428)	$ (105,531)	$ (36,433)	$ (53,632)
Investing activities	68,804	(69,407)	18,464	72,522
Financing activities	196,463	166,381	(133)	399

Net increase (decrease) in cash, cash equivalents and restricted cash	$ 125,839	(8,557)
Effect of exchange rates on cash	86	—
Net (decrease) increase in cash, cash equivalents and restricted cash	$ (18,016)	19,289

Net cash used in operating activities

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

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Net cash used in operating activities was $139.4 $36.4 million for the nine three months ended September 30, 2022 March 31, 2023 and consisted primarily of a net loss of $120.9 million $52.2 million adjusted for non-cash items of $9.9 million, which consisted of non-cash stock-based compensation, depreciation and amortization, rent expense and the change in the fair value of our embedded derivative liability. Our net loss also includes $5.4 million of acquired IPR&D assets, which are classified as investing activities. The change in operating assets and liabilities provided cash of approximately $0.4 million primarily driven by a net increase in accounts payable and accrued expenses of $5.2 million due to the timing of payments, offset by increases in accounts receivable and inventory of $4.5 million and a net increase in prepaid expenses and other assets of $0.3 million.

Net cash used in operating activities was $53.6 million for the three months ended March 31, 2022 and consisted primarily of a net loss of $52.8 million, adjusted for non-cash items of $4.9 million, 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 $4.9 million $5.8 million from a decrease an increase in other long-term assets prepaid expenses and other current assets coupled with a $13.7 million decrease in accounts payable, deferred revenue and accrued expenses and other current liabilities.

Net cash used in operating activities was $105.5 million for the nine months ended September 30, 2021 and consisted primarily of a net loss of $102.0 million adjusted for non-cash items, which consisted of non-cash stock-based compensation, the gain on the sale of the PRV, a deferred provision for income taxes, depreciation and amortization and rent expense. The change in operating assets and liabilities reflected a total use of cash of approximately $5.4 million from an increase in accounts payables and accrued expenses associated with our CROs, CMOs, and consultants due to the timing of payments, $6.7 million, offset by an increase a decrease of $8.9 million $0.9 million in prepaid expenses.

Net cash provided by (used in) investing activities

Net cash provided by investing activities was $68.8 million $18.5 million for the nine three months ended September 30, 2022 March 31, 2023 and relates to $224.6 million $92.7 million of maturities of short-term investments, partially offset by $151.5 million $69.6 million of purchases of short-term investments, a $4.0 million milestone obligation payment under our license agreement with Ipsen investments. We also used approximately $4.5 million to acquire Xinvento's IPR&D assets and $0.3 million related $0.1 million to the purchase of property plant and equipment.

Net cash used in provided by investing activities was $69.4 $72.5 million for the nine three months ended September 30, 2021 March 31, 2022 and relates to $164.0 million the $112.1 million of net maturities of short-term investments, offset by $39.5 million of purchases of short-term investments, $0.4 million and $0.1 million related to the purchase of property plant and equipment and $5.0 million for the acquisition equipment.

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Table of an intangible asset, partially offset by the $100.0 million in proceeds from the sale of the PRV. Contents

Net cash (used in) provided by financing activities

Net cash provided by used in financing activities was $196.5 million $0.1 million for the nine three months ended September 30, 2022 March 31, 2023, which represents the net proceeds comprised of $117.0 million from our common stock offering in September 2022, net proceeds from of $75.0 million from the a $1.3 million RIFA and $4.5 million payment partially offset by $1.2 million of cash proceeds from the exercise of stock options and the issuance of common stock from our 2017 Employee Stock Purchase Plan, or the ESPP.

Net cash provided by financing activities was $166.4 million $0.4 million for the nine three months ended September 30, 2021 March 31, 2022, which represents the net proceeds of $161.7 million from our common stock offering in February 2021 and $4.7 million of cash proceeds from the exercise of stock options and the issuance of common stock from the ESPP.

Revenue Interest Financing Agreement

On June 16, 2022, we announced a non-dilutive revenue interest financing agreement, Revenue Interest Financing Agreement, or RIFA, with HealthCare Royalty Partners, LLC, or HealthCare Royalty, for a total investment amount of up to $100 million. In exchange for the total investment amount to be received by Rhythm, HealthCare Royalty will receive a tiered royalty based on global net product sales generated by IMCIVREE. For additional information, see Note 10, 12, "Long-term Obligations" to the unaudited condensed consolidated financial statements included elsewhere in this Quarterly Report on Form 10-Q.

Funding requirements

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the clinical development of and seek marketing approval for setmelanotide for future indications and build out our global organization. In addition, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution to the extent that such sales, marketing and distribution are not the responsibility of potential collaborators. We also expect to incur additional costs associated with operating as a public company.

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We expect that our existing cash and cash equivalents and short-term investments will be sufficient to fund our operations into 2025. Our cash and cash equivalents are maintained at financial institutions in amounts that exceed federally-insured limits. In the event of failure of any of the financial institutions where we maintain our cash and cash equivalents, there can be no assurance that we will be able to access uninsured funds in a timely manner or at all.

We may need to obtain substantial additional funding in connection with our research and development activities and any continuing operations thereafter. If we are unable to raise capital when needed or on favorable terms, we would be forced to delay, reduce or eliminate our research and development programs or future commercialization efforts.

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

- the cost to commercialize setmelanotide, by building an internal sales force or entering into collaborations with third parties and providing support services for patients;
- the scope, progress, results and costs of clinical trials for our setmelanotide program;
- the costs, timing and outcome of regulatory review of our setmelanotide program;
- the obligations owed to Ipsen, Camurus and Takeda pursuant to our license agreements;
- the obligations owed to Xinvento pursuant to our purchase agreement
- the extent to which we acquire or in-license other product candidates and technologies;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- our ability to establish and maintain additional collaborations on favorable terms, if at all; and

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- the costs of operating as a public company, including those resulting from losing our emerging growth company status.

Although IMCIVREE has been approved by the FDA and authorized by the EC and Great Britain in certain indications, IMCIVREE may not achieve commercial success. In addition, developing our setmelanotide program is a time-consuming, expensive and uncertain process that may take years to complete, and we may never generate the necessary data or results required to obtain future marketing approvals and achieve product sales. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all.

In addition, the magnitude and duration impact of the COVID-19 pandemic and its impact on our liquidity and future funding requirements is uncertain as of the filing date of this Quarterly Report as this continues to evolve globally. evolve. See "Impact of COVID-19" above and "Risk Factors— The COVID-19 pandemic has and may continue to adversely impact our business, including our preclinical studies, clinical trials and our commercialization prospects." in Part II, Item 1A of this Quarterly Report for a further discussion of the possible impact of the COVID-19 pandemic on our business.

Further, the global economy, including credit and financial markets, has recently experienced extreme volatility and disruptions, including severely diminished liquidity and credit availability, rising interest and inflation rates, declines in

consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. All of these factors could impact our liquidity and future funding requirements, including but not limited to our ability to raise additional capital when needed on acceptable terms, if at all. The duration of this economic slowdown is uncertain and the impact on our business is difficult to predict. See "Risk Factors— Unfavorable global political or economic conditions could adversely affect our business, financial condition or results of operations."

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

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

If we raise funds through additional collaborations, strategic alliances or licensing arrangements with third parties or other means, we may have to relinquish valuable rights to our setmelanotide program on terms that may not be favorable to us. If we are unable to raise additional funds through equity, debt financings or other means, when needed, we may be

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required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market our setmelanotide program that we would otherwise prefer to develop and market ourselves.

Contractual obligations

As of September 30, 2022 March 31, 2023, apart from additional contractual obligations under our RIFA acquisition of Xinvento as disclosed in Note 10, "Long-Term Obligations" 3, "Asset Acquisition", to the unaudited condensed consolidated financial statements included under Part I, Item 1 of this Quarterly Report on Form 10-Q, there were no other 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, 2021 December 31, 2022.

Recent Accounting Pronouncements

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

Item 3. Quantitative and Qualitative Disclosures About Market Risk

As of September 30, 2022 March 31, 2023, 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, 2021 December 31, 2022.

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Item 4. Controls and Procedures

Limitations on Effectiveness of Controls and Procedures

In designing and evaluating our disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives. In addition, the design of disclosure controls and procedures must reflect the fact that there are resource constraints and that management is required to apply judgment in evaluating the benefits of possible controls and procedures relative to their cost.

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our principal executive officer and principal financial officer, has evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13a- 15(e) and 15d- 15(e) under the Securities Exchange Act of 1934, as amended), as of the end of the period covered by this Quarterly Report on Form 10-Q. Based on such evaluation, our principal executive officer and principal financial officer have concluded that, as of September 30, 2022 March 31, 2023, our disclosure controls and procedures were effective at the reasonable assurance level.

Changes in Internal Control Over Financial Reporting

There were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) that occurred during the most recent fiscal quarter covered by this Quarterly Report on Form 10-Q that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

PART II - OTHER INFORMATION

Item 1. Legal Proceedings

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

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Item 1A. Risk Factors

Our operations and financial results are subject to various risks and uncertainties, including those described below, which could adversely affect our business, financial condition, results of operations, cash flows, and the trading price of our common stock. Additional risks and uncertainties that we currently do not know about or that we currently believe to be immaterial may also impair our business. You should carefully consider the risks described below and the other information in this Annual Report, including our audited consolidated financial statements and the related notes thereto, and "Management's Discussion and Analysis of Financial Condition and Results of Operations."

Risks Related to Our Financial Position and Need for Capital

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

We are a commercial stage biopharmaceutical company with a limited operating history on which to base your investment decision. Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. We were incorporated in February 2013. Our operations to date have been primarily focused on developing and commercializing IMCIVREE® (setmelanotide) to treat patients living with hyperphagia and severe obesity caused by rare MC4R pathway diseases. Our business activities have included acquiring rights to intellectual property, business planning, raising capital, developing our technology, identifying potential product candidates, undertaking preclinical studies and conducting research and development activities, including clinical trials, for setmelanotide. To date we have generated less than $15.0 million $35.0 million of revenue from product sales. In the United States, IMCIVREE is approved for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndromic

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obesity due to pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency as determined by a U.S. Food and Drug Administration (FDA)-approved test demonstrating variants in POMC, PCSK1 or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance, or Bardet-Biedl syndrome (BBS). The European Commission (EC) has authorized setmelanotide for the treatment of obesity and the control of hunger associated with genetically confirmed BBS or genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. The UK's Medicines & Healthcare Products Regulatory Agency (MHRA) authorized setmelanotide for the treatment of obesity and the control of hunger associated with genetically confirmed BBS or genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above.

We have not obtained any other regulatory approvals for setmelanotide. We first commercialized IMCIVREE in the U.S. in the first quarter of 2021 and therefore do not have a long history operating as a commercial company. We are continuing to transition from a company with a research and development focus to a company capable of supporting commercial activities and we may not be successful in such transition. We are still at the early stages of demonstrating our ability to manufacture at commercial scale, or arrange for a third party to do so on our behalf, or conduct sales, marketing and distribution activities necessary for successful product commercialization. Consequently, any predictions made about our future success or viability may not be as accurate as they could be if we had a longer operating history.

Since our inception, we have focused substantially all of our efforts and financial resources on the research and development of setmelanotide, which is approved by the FDA and authorized by the EC and the MHRA, as noted above, and is in development to address patients affected by several other indications. We have funded our operations to date primarily through the proceeds from the sales of common stock and preferred stock, asset sales, as well as capital contributions from our former parent, Rhythm Holdings LLC, and have incurred losses in each year since our inception.

Our net losses were $40.9 million, $35.1 million, $138.6 million $52.2 million and $26.7 million $52.8 million for the three and nine months ended September 30, 2022 March 31, 2023 and 2021, 2022, respectively. As of September 30, 2022 March 31, 2023, we had an accumulated deficit of $667.6 million $762.2 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

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additional clinical trials of setmelanotide and development of any other product candidates we may choose to pursue. In addition, having obtained marketing approval for IMCIVREE, we expect to continue to incur significant sales, marketing and outsourced manufacturing expenses. We have and will continue to incur additional costs associated with operating as a public company, including as a result of no longer qualifying as an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. company. As a result, we expect to continue to incur significant and increasing operating losses for the foreseeable future. Because of the numerous risks and uncertainties associated with developing pharmaceutical products, we are unable to predict the extent of any future losses or when we will become profitable, if at all. Even if we do become profitable, we may not be able to sustain or increase our profitability on a quarterly or annual basis.

Our ability to become profitable depends upon our ability to generate revenue. To date we have generated less than $15.0 million $35.0 million of revenue from product sales. Our ability to generate revenue depends on a number of factors, including, but not limited to, our ability to:

- continue to commercialize setmelanotide by building a commercial organization and/or entering into collaborations with third parties;
- ensure setmelanotide is available to patients;
- continue to achieve market acceptance of setmelanotide in the medical community and with third-party payors;
- continue to initiate and successfully complete later-stage clinical trials that meet their clinical endpoints;

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- continue to initiate and successfully complete all safety studies required to obtain U.S. and foreign marketing approvals for setmelanotide as a treatment for obesity caused by genetic deficiencies affecting the MC4R pathway; and
- successfully manufacture or contract with others to manufacture setmelanotide.

Absent our entering into collaboration or partnership agreements, we have and expect to continue to incur significant sales and marketing costs as we prepare continue to commercialize setmelanotide. Even though IMCIVREE is FDA approved for chronic weight management in patients 6 years of age and older with monogenic or syndromic obesity due to POMC, PCSK1, or LEPR, deficiency confirmed by FDA-approved test demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted

as pathogenic, likely pathogenic, or of uncertain significance, and due to BBS and authorized in by the EU EMA and MHRA for the treatment of obesity and the control of hunger associated with genetically confirmed BBS, genetically confirmed loss-of-function biallelic POMC including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above, and for the treatment of patients with POMC or LEPR deficiency who have mild, moderate or severe renal impairment, and has received MHRA marketing authorization in the UK for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above, certain indications, and even if we successfully complete our pivotal and other clinical trials and setmelanotide is approved for commercial sale in additional indications, setmelanotide may not be a commercially successful drug. As of result of the acquisition of Xinvento B.V., we expect to devote substantial financial resources to the research and development and potential commercialization of a therapeutic product candidate for CHI. We may not achieve profitability soon after generating product sales, if ever. If we are unable to generate significant product revenue, we will not become profitable and will be unable to continue operations without continued funding.

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

We are currently in the early stages of commercializing IMCIVREE for chronic weight management in patients with obesity due to BBS, POMC, PCSK1 or LEPR deficiencies in the U.S. and the EU and Great Britain and advancing setmelanotide through clinical development for additional indications in the United States and for potential approvals in

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other countries. Developing peptide therapeutic products is expensive and we expect our research and development expenses to increase substantially in connection with our ongoing activities, particularly as we advance setmelanotide in additional clinical trials. trials, as well as in connection with research and development activities as a result of the acquisition of Xinvento B.V. in February 2023. We intend to use our available cash resources to advance the clinical development of setmelanotide, for disease-education and community-building activities, patient identification, and commercialization activities related to IMCIVREE. Depending on the status of additional regulatory approvals and commercialization of setmelanotide, as well as the progress we make in any sales of IMCIVREE, we may still require significant additional capital to fund the continued development of setmelanotide and our operating needs thereafter. We may also need to raise additional funds if we choose to pursue additional indications and/or geographies for setmelanotide or otherwise expand more rapidly than we presently anticipate.

From August 2015 through August 2017, we raised aggregate net proceeds of $80.8 million through our issuance of series A preferred stock. In connection with our initial public offering, or IPO, in October 2017 and our underwritten follow-on offerings through October 2022, we raised aggregate net proceeds of approximately $742.6 million through the issuance of our common stock after deducting underwriting discounts, commissions and offering related transaction costs. Since inception, we have We received a further $100.0 million from asset sales, specifically in connection with the sale of our Rare Pediatric Disease Priority Review Voucher, or PRV, to Alexion Pharmaceuticals, Inc. In June 2022, we entered into the a Revenue Interest Financing Agreement, or RIFA, with HealthCare Royalty Partners for a total investment amount of up to $100 million $100.0 million, conditioned upon our achievement of certain clinical development and sales milestones.As of September 30, 2022 March 31, 2023, we have received $72.3 million of aggregate proceeds, net of debt issuance costs, under the RIFA. As of March 31, 2023, our cash and cash equivalents and short-term investments were approximately $347.8 million $294.6 million. We expect that our existing cash and cash equivalents and short-term investments will be sufficient to fund our operations into 2025. However, our

operating plan may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through public or private equity or debt financings, government or other third party third-party funding, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements, or a combination of these approaches. We will also require additional capital to obtain additional regulatory approvals for, and to continue to commercialize, setmelanotide. Raising funds in the current economic environment, particularly in light of ongoing uncertainty related to the COVID-19 pandemic, supply chain issues and labor shortages, rising inflation and interest rates and international turmoil, including due to the Russian invasion of Ukraine, may present additional challenges. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or if we have specific strategic considerations.

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The Company maintains the majority of its cash and cash equivalents in accounts with major U.S. and multi-national financial institutions, and our deposits at certain of these institutions exceed insured limits. Market conditions can impact the viability of these institutions. In the event of failure of any of the financial institutions where we maintain our cash and cash equivalents, there can be no assurance that we would be able to access uninsured funds in a timely manner or at all. Any inability to access or delay in accessing these funds could adversely affect our business and financial position.

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

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

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

On June 16, 2022, we entered into the RIFA with entities managed by HealthCare Royalty Management, collectively referred to as the Investors. Pursuant to the RIFA and subject to customary closing conditions, the Investors

have agreed to pay the Company an aggregate investment amount of up to $100.0 million, or the Investment Amount. Under the terms of the RIFA, we received $37.5 million on June 29, 2022 upon FDA approval of IMCIVREE in BBS, and an additional $37.5 million on September 29, 2022, following EC marketing authorization for BBS on September 6, 2022. We are entitled to receive the remaining $25.0 million of the Investment Amount forty-five business days following achievement of a specified amount of cumulative net sales of IMCIVREE between July 1, 2022 and September 30, 2023.

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

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

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

- increasing our vulnerability to adverse economic and industry conditions;
- limiting our ability to obtain additional financing or enter into IMCIVREE partnership agreements;
- requiring the dedication of a portion of our cash flow from operations to service our indebtedness, which will reduce the amount of cash available for other purposes;
- limiting our flexibility to plan for, or react to, changes in our business;
- placing us at a possible competitive disadvantage with competitors that are less leveraged than us or have better access to capital; and

- if we fail to comply with the terms of the RIFA, resulting in an event of default that is not cured or waived, Investors could seek to enforce their security interest in our cash and cash equivalents and all assets relating to IMCIVREE that secures such indebtedness.

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

Risks Related to the Development of Setmelanotide

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

Positive results from any of our Phase 1, Phase 2, or Phase 3 clinical trials of setmelanotide, or initial results from other clinical trials of setmelanotide, may not be predictive of the results of later clinical trials. The duration of effect of setmelanotide tested in our Phase 1 and Phase 2 clinical trials was often for shorter periods than in our pivotal Phase 3

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

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

We are actively working to advance additional genetic variants related to the MC4R pathway through our clinical development program. Our continued development efforts are focused on obesity related to several single gene related, or monogenic, MC4R pathway impairments: BBS; HET obesity due to a genetic variant in one of the two alleles of the *POMC*, *PCSK1* or *LEPR* gene, or HETs; obesity due to steroid receptor coactivator 1, or SRC1, variants; obesity due to SH2B adapter protein 1, or SH2B1; hypothalamic obesity; and MC4R deficiency obesity. For example, in April 2022 we enrolled the first patient our pivotal Phase 3 EMANATE clinical trial of setmelanotide. The trial is a randomized, double-blind,

placebo-controlled study with four independent sub-studies evaluating setmelanotide in patients with: heterozygous POMC/PCSK1 obesity; heterozygous LEPR obesity; certain variants of the SRC1; or certain variants of SH2B1 genes. After receiving feedback from the FDA in April 2022 that indicated that additional clinical trials to support potential registration for non-rare patient populations would likely be required, we eliminated a fifth sub-study intended to evaluate setmelanotide in patients with a PCSK1 N221D variant. Each of the four sub-studies will be entirely independent of the others and, if successful, is designed to support separate regulatory submissions to the FDA and EMA in each studied indication. However, the FDA and EMA may not view positive results in one sub-study, even if such results are statistically significant and clinically meaningful, as being sufficient for approval for any given indication. indication.

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

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

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

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

From time to time, we may publicly disclose preliminary or topline data from our preclinical studies and clinical trials, which is based on a preliminary analysis of then-available data, and the results and related findings and conclusions

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are subject to change following a more comprehensive review of the data related to the particular study or trial. We make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, the topline or preliminary results that we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. Topline data also remain subject to audit and verification procedures that may

result in the final data being materially different from the preliminary data we previously published or reported. As a result, topline data should be viewed with caution until the final data are available.

From time to time, we may also disclose interim data from our preclinical studies and clinical trials. Interim data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. Adverse differences between preliminary or interim data and final data could significantly harm our business prospects. Further, disclosure of interim data by us or by our competitors could result in volatility in the price of our common stock.

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

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

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

Due to the rarity of our target indications, there is no comprehensive patient registry or other method of establishing with precision the actual number of patients with MC4R pathway deficiencies. As a result, we have had to rely on other available sources to derive clinical prevalence estimates for our target indications. In addition, we have internal genetic sequencing results from individuals with severe obesity that provide another approach to estimating prevalence. As of December 31, 2021 December 31, 2022, our database had approximately 45,000 60,000 sequencing samples. Since the published epidemiology studies for these genetic variants are based on relatively small population samples, and are not amenable to robust statistical analyses, it is possible that these projections may significantly exceed the addressable population, particularly given the need to genotype patients to definitively confirm a diagnosis.

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

- *POMC Deficiency Obesity*. POMC Deficiency Obesity is defined by the presence of biallelic variants in the *POMC* or *PCSK1* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance. Our addressable patient population estimate for POMC deficiency obesity is approximately 100 to 500 patients in the United States, with a comparable addressable patient population in Europe. Our estimates are based on:

- approximately 50 patients with POMC deficiency obesity noted in a series of published case reports, each mostly reporting a single or small number of patients. However, we believe our addressable patient population for this deficiency may be approximately 100 to 500 patients in the United States, and a comparable addressable patient population in Europe, as most of the reported cases are from a small number of academic research centers, and because genetic testing for POMC deficiency obesity is often unavailable and currently is rarely performed;

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- our belief, based on discussions with experts in rare diseases, that the number of diagnosed cases could increase several-fold with increased awareness of this deficiency and the availability of new treatments;
- U.S. Census Bureau figures for adults and children, and Centers for Disease Control and Prevention, or CDC, prevalence numbers for adults with severe obesity (body mass index, or BMI, greater than 40 kg/m2) and for children with severe early-onset obesity (99th percentile at ages two to 17 years old); and
- our internal sequencing yield for POMC deficiency obesity patients (including both*POMC* and *PCSK1*gene diseases), defined as patients having biallelic variants in the *POMC* or *PCSK1* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance, of approximately 0.05%.

- *LEPR Deficiency Obesity*. LEPR Deficiency Obesity is defined by the presence of biallelic variants in the *LEPR* gene that are interpreted as pathogenic, likely pathogenic, or of uncertain significance. Our addressable patient population estimate for LEPR deficiency obesity is approximately 500 to 2,000 patients in the United States, with a comparable addressable patient population in Europe. Our estimates are based on:
  - epidemiology studies on LEPR deficiency obesity in small cohorts of patients comprised of children with severe obesity and adults with severe obesity who have a history of early onset obesity;

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- U.S. Census Bureau figures for adults and children and CDC prevalence numbers for adults with severe obesity (BMI, greater than 40 kg/m2) and for children with severe early-onset obesity (99th percentile at ages two to 17 years old);
- with wider availability of genetic testing expected for LEPR deficiency obesity and increased awareness of new treatments, our belief that up to 40% of patients with these diseases may eventually be diagnosed; and
- our internal sequencing yield for LEPR deficiency obesity patients, defined as patients having biallelic variants in the *LEPR* gene that are interpreted as pathogenic, likely pathogenic, or of uncertain significance, of approximately 0.09%.

- *Bardet-Biedl Syndrome*. Our addressable patient population estimate for BBS is approximately 1,500 4,000 to 2,500 5,000 patients in the United States based on:

- published prevalence estimates of one in 100,000 in North America, which projects to approximately 3,250 people in the United States. We believe the majority of these patients are addressable patients;
- comparisons to our patient identification efforts in Europe where we believe there are approximately 1,500 patients diagnosed and being cared for at academic centers in Europe;
- our patient identification efforts to date in the United States;
- our internal sequencing yield for biallelic pathogenic or likely pathogenic variants in BBS genes of approximately 0.3%; and
- our belief that with wider availability of genetic testing expected for BBS and increased awareness of new treatments, the number of patients diagnosed with this disorder will increase.

- *POMC, PCSK1, or LEPR Heterozygous Obesities; SRC1 and SH2B1 Obesities*. Our potential setmelanotide-responsive patient population estimate for POMC, PCSK1, or LEPR heterozygous, SRC1 and SH2B1 obesity patients with at least one variant interpreted as pathogenic, likely pathogenic, or of uncertain significance suspected pathogenic is approximately 53,000 patients in the United States. Our estimates are based on:
  - U.S. Census Bureau population data and CDC prevalence numbers for early onset obesity (120% the 95th percentile between the ages of 2-5 years);
  - our internal sequencing yield of patients with POMC, PCSK1, or LEPR heterozygous, SRC1 or SH2B1 variants interpreted as pathogenic, likely pathogenic, or of uncertain significance of approximately 10-15%; and

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  - a clinical response rate of 40% for patients carrying pathogenic or likely pathogenic variants, and 20% for patients carrying a variant of uncertain significance.

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

- *MC4R Deficiency Obesity*. Our addressable patient population estimate for MC4R-rescuable deficiency obesity is approximately 10,000 patients in the United States. This estimate is based on:
  - U.S. Census Bureau population data and CDC prevalence numbers for early onset obesity (120% the 95th percentile between the ages of 2-5 years);

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  - a comprehensive ongoing biochemical screening study indicating there may be a defined subset of individuals who carry MC4R variants that may be rescued by an MC4R agonist; and

- our internal sequencing yield for MC4R deficiency obesity patients of approximately 2.0% prior to application of functional filters.

- *Hypothalamic obesity*. Our addressable patient population estimate for hypothalamic obesity (HO) is 5,000 to 10,000 patients in the United States. This estimate is based on:

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

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

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

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

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

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

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

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

If we experience delays or difficulties in the enrollment and/or retention of patients in clinical trials, our regulatory submissions or receipt of additional marketing approvals could be delayed or prevented.

We may not be able to initiate or continue our planned clinical trials on a timely basis or at all for our product candidates if we are unable to recruit and enroll a sufficient number of eligible patients to participate in these trials through

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completion of such trials as required by the FDA or other comparable foreign regulatory authorities. Patient enrollment is a significant factor in the timing of clinical trials. Our ability to enroll eligible patients may be limited or may result in slower enrollment than we anticipate.

Our clinical trials will compete with other clinical trials that are in the same therapeutic areas as our product candidates, including general obesity, and this competition reduces the number and types of patients available to us, as some patients who might have opted to enroll in our trials may instead opt to enroll in a trial being conducted by one of our competitors. Because the number of qualified clinical investigators and clinical trial sites is limited, we expect to conduct some of our clinical trials at the same clinical trial sites that some of our competitors use, which will reduce the number of patients who are available for our

clinical trials at such clinical trial sites. In addition, there are limited patient pools from which to draw for clinical studies. In addition to the rarity of genetic diseases of obesity, the eligibility criteria of our clinical studies will further limit the pool of available study participants as we will require that patients have specific

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characteristics that we can measure or to assure their disease is either severe enough or not too advanced to include them in a study. Patient enrollment for our current or any future clinical trials may be affected by other factors, including:

- size and nature of the patient population;
- severity of the disease under investigation;
- availability and efficacy of approved drugs for the disease under investigation;
- patient eligibility criteria for the trial in question as defined in the protocol;
- perceived risks and benefits of the product candidate under study;
- clinicians' and patients' perceptions as to the potential advantages of the product candidate being studied in relation to other available therapies, including any new products that may be approved or future product candidates being investigated for the indications we are investigating;
- clinicians' willingness to screen their patients for genetic markers to indicate which patients may be eligible for enrollment in our clinical trials;
- delays in or temporary suspension of the enrollment of patients in our planned clinical trial due to the COVID-19 pandemic; pandemic or other public health emergencies;
- ability to obtain and maintain patient consents;
- patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment;
- proximity and availability of clinical trial sites for prospective patients; and
- the risk that patients enrolled in clinical trials will drop out of the trials before completion, including as a result of contracting COVID-19 or other health conditions or being forced to quarantine, or, because they may be late-stage cancer patients or for other reasons, will not survive the full terms of the clinical trials.

In addition, the pediatric population is an important patient population for setmelanotide, and our addressable patient population estimates include pediatric populations. However, it may be more challenging to conduct studies in younger participants, and to locate and enroll pediatric patients. These factors may make it difficult for us to enroll enough patients to complete our clinical trials in a timely and cost-effective manner. Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays or may require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may also result in increased development costs for setmelanotide and

any future product candidates and jeopardize our ability to obtain additional marketing approvals for the sale of setmelanotide. Furthermore, even if we are able to enroll a sufficient number of patients for our clinical trials, we may have difficulty maintaining participation in our clinical trials through the treatment and any follow-up periods.

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

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

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

- inability to generate sufficient preclinical or other *in vivo* or *in vitro* data to support the initiation of clinical studies;
- delays in the completion of preclinical laboratory tests, animal studies and formulation studies in accordance with FDA's good laboratory practice requirements and other applicable regulations;
- the FDA or other equivalent competent authorities in foreign jurisdictions may deny permission to proceed with our ongoing or planned trials or any other clinical trials we may initiate, or may place a clinical trial on hold or be suspended;
- delays in filing or receiving authorization to proceed under an additional investigational new drug application, or IND, or similar foreign application if required;
- delays in reaching a consensus with the FDA and other regulatory agencies on study design and obtaining regulatory authorization to commence clinical trials;
- delays in reaching or failing to reach agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- difficulties in obtaining Institutional Review Board, or IRB, and/or ethics committee approval or opinion to conduct a clinical trial at a prospective site or sites;
- since many already diagnosed patients are at academic sites, delays in conducting clinical trials at academic sites due to the particular challenges and delays typically associated with those sites, as well as the lack of alternatives to these sites which have already diagnosed patients;

- inadequate quantity or quality of setmelanotide or other materials necessary to conduct clinical trials, including delays in the manufacturing of sufficient supply of finished drug product;
- challenges in identifying, recruiting and training suitable clinical investigators;
- challenges in recruiting and enrolling suitable patients to participate in clinical trials;
- severe or unexpected drug related side effects experienced by patients in a clinical trial, including side effects previously identified in our completed clinical trials;

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- difficulty collaborating with patient groups and investigators;
- failure by our CROs, other third parties or us to perform in accordance with the FDA's or any other regulatory authority's good clinical practice requirements, or GCPs, or applicable regulatory guidelines in other countries;
- occurrence of adverse events associated with setmelanotide that are viewed to outweigh its potential benefits, or occurrence of adverse events in trial of the same or similar class of agents conducted by other companies;
- changes to the clinical trial protocols;

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- clinical sites deviating from trial protocol or dropping out of a trial;
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols;
- changes in the standard of care on which a clinical development plan was based, which may require new or additional trials;
- selection of clinical endpoints that require prolonged periods of observation or analyses of resulting data;
- the cost of clinical trials of our product candidates being greater than we anticipate;
- clinical trials of our product candidates producing negative or inconclusive results, which may result in our deciding, or regulators requiring us, to conduct additional clinical trials or abandon development of such product candidates; and
- development of antibodies to the drug or adjuvants may result in loss of efficacy or safety events.

In addition, disruptions caused by the COVID-19 pandemic and other public health emergencies may increase the likelihood that we encounter such difficulties or delays in initiating, enrolling, conducting or completing our planned and ongoing clinical trials. Clinical trials may also be delayed or terminated as a result of ambiguous or negative interim results. In

addition, a clinical trial may be suspended or terminated by us, the FDA or other equivalent competent authorities in foreign jurisdictions, the IRB at the sites where the IRBs are overseeing a clinical trial, a data and safety monitoring board, or DSMB, or Safety Monitoring Committee, or SMC, overseeing the clinical trial at issue or other equivalent competent authorities due to a number of factors, including, among others:

- failure to conduct the clinical trial in accordance with regulatory requirements or our clinical trial protocols;
- inspection of the clinical trial operations or trial sites by the FDA or other equivalent competent authorities that reveals deficiencies or violations that require us to undertake corrective action, including the imposition of a clinical hold;
- unforeseen safety issues, adverse side effects or lack of effectiveness;
- changes in government regulations or administrative actions;
- problems with clinical trial supply materials; and
- lack of adequate funding to continue the clinical trial.
- Delays in the completion of any preclinical studies or clinical trials of setmelanotide will increase our costs, slow down our product candidate development and approval process and delay or potentially jeopardize our

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

In addition, the FDA's and other regulatory authorities' policies with respect to clinical trials may change and additional government regulations may be enacted. For instance, the regulatory landscape related to clinical trials in the EU recently evolved. The EU Clinical Trials Regulation (CTR) which was adopted in April 2014 and repeals the EU Clinical Trials Directive, became applicable on January 31, 2022. While the EU Clinical Trials Directive required a separate clinical trial application (CTA) to be submitted in each member state, to both the competent national health

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

authority and an independent ethics committee, the EU CTR introduces a centralized process and only requires the submission of a single application to all member states concerned. The COVID-19 pandemic EU CTR allows sponsors to make a single submission to both the competent authority and an ethics committee in each member state, leading to a single

decision per member state. The assessment procedure of the CTA has been harmonized as well, including a joint assessment by all member states concerned, and may continue a separate assessment by each member state with respect to adversely impact our business, specific requirements related to its own territory, including our preclinical studies, clinical trials and our commercialization prospects.

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

- delays in receiving approval from local regulatory authorities to initiate or conduct our planned clinical trials;
- further delays or difficulties in enrolling patients in our clinical trials;
- delays or difficulties in clinical site initiation, including difficulties in recruiting clinical site investigators and clinical site staff;
- further delays in clinical sites receiving the supplies and materials needed to conduct our clinical trials, including interruption in global shipping that may affect the transport of clinical trial materials;
- changes in local regulations as part of a response to the COVID-19 pandemic which may require us to change the ways in which our clinical trials are conducted, which may result in unexpected costs, or to discontinue such clinical trials altogether;
- diversion of healthcare resources away from the conduct of clinical trials, including the diversion of hospitals serving as our clinical trial sites and hospital staff supporting the conduct of our clinical trials;
- further interruption of key clinical trial activities, such as clinical trial site monitoring, due to limitations on travel imposed or recommended by federal or state governments, employers and others, or interruption of clinical trial subject visits and study procedures, the occurrence of which could affect the integrity of clinical trial data;
- risk that participants enrolled in our clinical trials will contract COVID-19 while the clinical trial is ongoing, which could impact the results of the clinical trial, including by increasing the number of observed adverse events;
- interruptions or delays in preclinical studies due to restricted or limited operations at our research and development laboratory facility;

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- interruptions or delays in manufacturing activities due to restricted or limited operations at our CMOs;
- delays in global shipping of raw materials, API, and/or finished goods between locations;
- interruptions or delays in delivery of clinical trial ancillary supplies, due to restricted or limited operations;
- delays in necessary interactions with local regulators, ethics committees and other important agencies and contractors due to limitations in employee resources or forced furlough of government employees;
- continued limitations in employee resources that would otherwise be focused on the start-up or conduct of our clinical trials, including because of sickness of employees or their families or the desire of employees to avoid contact with large groups of people, or due to increased hiring and/or retention or other staffing issues;
- refusal of the FDA or foreign regulatory authorities to accept data from clinical trials in affected geographies;
- impacts from prolonged remote work arrangements, such as increased cybersecurity risks and strains on our business continuity plans; and
- delays in the receipt of marketing authorizations for our product candidates, which could materially affect our commercialization plans.

The COVID-19 pandemic continues to rapidly evolve. three-year transition period. The extent to which the pandemic impacts our business, preclinical studies, ongoing and new clinical trials will be governed by the EU CTR varies. For clinical trials whose CTA was made under the EU Clinical Trials Directive before January 31, 2022, the EU Clinical Trials Directive will continue to apply on a transitional basis until January 31, 2025. Clinical trials for which an application was submitted (i) prior to January 31, 2022 under the EU Clinical Trials Directive, or (ii) between January 31, 2022 and January 31, 2023 and for which the sponsor has opted for the application of the EU Clinical Trials Directive remain governed by said Directive until January 31, 2025. After this date, all clinical trials (including those which are ongoing) will become subject to the provisions of the EU CTR. Compliance with the EU CTR requirements by us and our commercialization prospects will depend on future developments, which are highly uncertain and cannot be predicted with confidence, third-party service providers, such as CROs, may impact our developments plans.

If we are slow or unable to adapt to changes in existing requirements or the duration and severity adoption of the pandemic, the impact of the variants, travel restrictions and social distancing recommendations and regulations in the United States and other countries, business closures new requirements or business disruptions, the effectiveness of vaccines, vaccine distribution efforts and treatments, and the effectiveness of other actions taken in the United States and other countries to contain and treat the disease. While the potential economic impact brought by and the duration of the COVID-19 pandemic policies governing clinical trials, our development plans 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. impacted.

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

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

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

- adverse effects on cardiovascular parameters, such as increases in heart rate and blood pressure;
- erections in males and similar effects in women, such as sexual arousal, clitoral swelling and hypersensitivity;
- nausea and vomiting;

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- reduced appetite;
- headache;
- effects on mood, depression, anxiety and other psychiatric manifestations; and
- other effects, for which most investigators reported as unrelated to setmelanotide and for which no increased incidence or pattern is currently evident.

In addition, injection site reactions have been seen in subcutaneous, or SC, injections with setmelanotide. In addition, Also, setmelanotide has likely off target effects on the closely related MC1 receptor, which mediates tanning in response to sun exposure. Other MC1 receptor mediated effects include darkening of skin blemishes, such as freckles and moles, and hair color change. The cosmetic effects are not tolerated by all patients, as a small number of patients have withdrawn from

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treatment due to skin darkening. These effects have generally been reversible in clinical trials after discontinuation of setmelanotide, but it is still unknown if they will be reversible with long term exposure. The MC1 receptor mediated effects may also carry risks. The long term impact of MC1 receptor activation has not been tested in clinical trials, and could potentially include increases in skin cancer, excess biopsy procedures and cosmetic blemishes. These skin changes may also result in unblinding, which could make interpretation of clinical trial results more complex and possibly subject to bias. We have also initiated trials of setmelanotide in potential new indications that include patients who might have more serious underlying conditions, such as Alström syndrome and other indications. conditions. It is possible that the underlying conditions in these patients, such as congestive heart failure and potentially other conditions, may confound the understanding of the safety profile of setmelanotide.

If these or other significant adverse events or other side effects are observed in any of our ongoing or planned clinical trials, we may have difficulty recruiting patients to the clinical trials, patients may drop out of our trials, or we may be required to abandon the trials or our development efforts of that product candidate altogether. We, the FDA, other comparable regulatory authorities or an IRB may also suspend clinical trials of a product candidate at any time for various reasons, including

a belief that subjects in such trials are being exposed to unacceptable health risks or adverse side effects. Some potential therapeutics developed in the biotechnology industry that initially showed therapeutic promise in early-stage trials have later been found to cause side effects that prevented their further development. Even if the side effects do not preclude setmelanotide from maintaining marketing approval or obtaining additional approvals, undesirable side effects may inhibit market acceptance due to its tolerability versus other therapies. Any of these developments could materially adversely affect our business, financial condition and prospects.

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

- regulatory authorities may request that we withdraw the product from the market or may limit or vary their approval of the product through labeling or other means;
- regulatory authorities may require the addition of labeling statements, such as a "boxed" warning or a contraindication;
- the FDA, the EU competent authorities and other equivalent competent authorities in foreign jurisdictions may require the addition of a Risk Evaluation and Mitigation Strategy, or REMS, or other specific obligations as a condition for marketing authorization due to the need to limit treatment to rare patient populations, or to address safety concerns;
- we may be required to change the way the product is distributed or administered or change the labeling of the product;
- we may be required to conduct additional studies and clinical trials or comply with other post-market requirements to assess possible serious risks;

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- 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.

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We may not be able to obtain or maintain orphan drug designations for setmelanotide or to obtain or maintain exclusivity in any use. Even with exclusivity, competitors may obtain approval for different drugs that treat the same indications as setmelanotide.

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

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

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

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

Grant of orphan designation by the EC also entitles the holder of this designation to financial incentives such as reduction of fees or fee waivers, protocol assistance, and access to the centralized marketing authorization procedure. Orphan drug designation must be requested before submitting an application for marketing authorization. In addition to a range of other benefits during the development and regulatory review, orphan medicinal products are, upon grant of marketing authorization, entitled to ten years of exclusivity in all EU member states for the approved therapeutic indication, which means that the competent authorities cannot accept another marketing authorization application, grant a marketing authorization, or accept an application to extend a marketing authorization for a similar product for the same indication

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for a period of ten years. The period of market exclusivity is extended by two years for orphan medicinal products that have also complied with an agreed Pediatric Investigation Plan, or PIP. No extension to any supplementary protection certificate can be granted on the basis of pediatric studies for orphan indications. Orphan medicinal product designation does not convey any

advantage in, or shorten the duration of, the regulatory review and approval process. Marketing authorization may, however, be granted to a similar medicinal product with the same orphan indication during the ten-year period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities.

The ten-year market exclusivity in the EU may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for which it received orphan designation, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity, or where the prevalence of the condition has increased above the threshold. Additionally granting of an authorization for another similar orphan medicinal product where another product has market exclusivity can happen at any time: (i) the second applicant can

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establish that its product, although similar, is safer, more effective or otherwise clinically superior; (ii) the applicant cannot supply enough orphan medicinal product or (iii) where the applicant consents to a second orphan medicinal product application. Orphan drug designation does not, in itself, convey any advantage in, or shorten the duration of, the regulatory review and authorization process.

In connection with IMCIVREE's approval, the FDA granted us seven years of orphan drug exclusivity for setmelanotide for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to POMC, PCSK1, or LEPR deficiency and BBS confirmed by genetic testing demonstrating variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance, and in the EU, we obtained ten years of market exclusivity for setmelanotide for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above.

We have also been granted orphan drug designation for setmelanotide for the treatment of BBS and Alström syndrome in both the United States and the EU. Setmelanotide has also been granted orphan designation for setmelanotide in treating Prader-Willi syndrome in the EU. There can be no assurance that we will be able to maintain the benefits orphan drug exclusivity, or that the FDA or the EC will grant orphan designations for setmelanotide for other uses. In addition, orphan drug designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process.

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

Although we have obtained PRIME designation in the EU for setmelanotide for the treatment of obesity and the control of hunger associated with deficiency disorders of the MC4R receptor pathway and Breakthrough Therapy designation for setmelanotide for the treatment of obesity associated with certain genetic defects upstream of the MC4R in the leptin melanocortin pathway, which includes POMC deficiency obesity, LEPR deficiency obesity, Bardet- Biedl Bardet-Biedl syndrome and Alström syndrome, as well as hypothalamic obesity in the United States, the FDA may rescind the Breakthrough Therapy designation and we may be unable to obtain Breakthrough Therapy designation for other uses. In

addition, Breakthrough Therapy designation by the FDA or PRIME designation by the EMA may not lead to a faster development, regulatory review or approval process, and it does not increase the likelihood that setmelanotide will receive additional marketing approvals in the United States or additional marketing authorizations in the EU.

The FDA is authorized under the FDCA to give certain product candidates "Breakthrough Therapy designation." A Breakthrough Therapy product candidate is defined as a product candidate that is intended, alone or in combination with one or more other drugs, to treat a serious or life threatening disease or condition and preliminary clinical evidence indicates that such product candidate may demonstrate substantial improvement on one or more clinically significant endpoints over existing therapies. The FDA will seek to ensure the sponsor of Breakthrough Therapy product candidate

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receives intensive guidance on an efficient drug development program, intensive involvement of senior managers and experienced staff on a proactive, collaborative and cross disciplinary review. In addition, the FDA may consider reviewing portions of an NDA before the sponsor submits the complete application, or rolling review. Product candidates designated as breakthrough therapies by the FDA may be eligible for other expedited programs, such as priority review, if supported by clinical data.

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

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The PRIME scheme was launched by the EMA in 2016. In the EU, innovative products that target an unmet medical need and are expected to be of major public health interest may be eligible for a number of expedited development and review programs, such as the PRIME scheme, which provides incentives similar to the Breakthrough Therapy designation in the United States. PRIME is a voluntary scheme aimed at enhancing the EMA's support for the development of medicines that target unmet medical needs. It is based on increased interaction and early dialogue with companies developing promising medicines, to optimize their product development plans and speed up their evaluation to help them reach patients earlier. The benefits of a PRIME designation include the appointment of a rapporteur before submission of a marketing authorization application, early dialogue and scientific advice at key development milestones, and the potential to qualify products for accelerated review

earlier in the application process. In late June 2018, setmelanotide was granted eligibility to PRIME by the CHMP for the treatment of obesity and the control of hunger associated with deficiency disorders of the MC4R receptor pathway. Acknowledging that setmelanotide targets an unmet medical need, the EMA offers enhanced support in the development of the medicinal product through enhanced interaction and early dialogue to optimize our development plans and speed up regulatory evaluation in the EU. As part of this designation, the EMA has provided guidance to us concerning the development of setmelanotide. The PRIME designation does not, however, guarantee that the regulatory review process in the EU will be shorter or less demanding. Neither does the PRIME designation guarantee that the EC will grant additional marketing authorizations for setmelanotide.

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

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

We have entered into a license agreement with Camurus AB, or Camurus, for the use of Camurus' drug delivery technology, FluidCrystal, to formulate once-weekly setmelanotide. This formulation, if successfully developed for setmelanotide, and approved by the FDA and other regulatory authorities, will be delivered subcutaneously, similar to our once-daily formulation, except that we anticipate it will be injected once weekly. In addition, we have initiated development of an auto-injector device designed to make administration of our once-weekly product candidate easier and more convenient for our patients.

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

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

Our approach to treating patients with MC4R pathway deficiencies requires the identification of patients with unique genetic subtypes, for example, POMC genetic deficiency. The FDA or other equivalent competent authorities in foreign jurisdictions could require the clearance, approval or certification of an in vitro companion diagnostic device to ensure appropriate selection of patients as a condition of approving setmelanotide in additional indications. The requirement that we obtain clearance, approval or certification of an in vitro companion diagnostic device will require substantial financial

resources, and could delay or prevent the receipt of additional regulatory approvals for setmelanotide, or adversely affect those we have already obtained.

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

In the EU, until May 25, 2022, in vitro diagnostic medical devices were regulated by Directive 98/79/EC, or the IVDD, which has been repealed and replaced by Regulation (EU) No 2017/746, or the IVDR. Unlike the IVDD, the IVDR is directly applicable in EU member states without the need for member states to implement into national law. The regulation of companion diagnostics is now subject to further requirements set forth in the IVDR. However on October 14, 2021, the EC proposed a "progressive" roll-out of the IVDR to prevent disruption in the supply of in vitro diagnostic medical devices. The European Parliament and Council adopted the proposed regulation on December 15, 2021. The IVDR became applicable on May 26, 2022 but there is a tiered system extending the grace period for many devices (depending on their risk classification) before they have to be fully compliant with the regulation. For instance, class C devices (including devices that are intended to be used as companion diagnostics) have until May 26, 2026 to comply with the new requirements. The IVDR introduces a new classification system for companion diagnostics which are now specifically defined as diagnostic tests that support the safe and effective use of a specific medicinal product, by identifying patients that are suitable or unsuitable for treatment. Companion diagnostics will have to undergo a conformity assessment by a notified body. Before it can issue a CE an EU certificate, the notified body must seek a scientific opinion from the EMA on the suitability of the companion diagnostic to the medicinal product concerned if the medicinal product falls exclusively within the scope of the centralized procedure for the authorization of medicines, or the medicinal product is already authorized through the centralized procedure, or a marketing authorization application for the medicinal product has been submitted through the centralized procedure. For other substances, the notified body can seek the opinion from a national competent authorities or the EMA. Compliance with the new requirements may impact our development plans for setmelanotide.

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If the FDA or a comparable regulatory authority requires clearance, approval or certification of a companion diagnostic for setmelanotide, any delay or failure by us or our current and future collaborators to develop or obtain regulatory clearance

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

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novo request seeking FDA authorization to market such an *in vitro* companion diagnostic device for IMCIVREE as a Class II medical device. In January 2022, the FDA granted the *de novo* request for classification for the POMC/PCSK1/LEPR CDx Panel for market authorization as a Class II device. In June 2022, the FDA approved our supplemental NDA for the use of IMCIVREE to treat chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to BBS. If the FDA or a comparable regulatory authority requires clearance, approval or certification of a companion diagnostic when we seek additional approvals for setmelanotide, any delay or failure by us or our current and future collaborators to develop or obtain regulatory clearance or approval of, or certification of, such tests, if necessary, could delay or prevent us from obtaining such additional approvals for setmelanotide, or adversely affect the approvals we have already obtained.

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

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

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

These factors, among others, may materially adversely affect the willingness or ability of third parties to conduct our clinical trials and may subject us to unexpected cost increases that are beyond our control. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards, and our reliance on CROs does not relieve us of our regulatory responsibilities. We and our CROs are required to comply with GCPs, which are guidelines enforced by the FDA, the competent authorities of the EU member states and equivalent competent authorities in foreign jurisdictions for any products in clinical development. The FDA and

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foreign regulatory authorities enforce these regulations and GCP guidelines through periodic inspections of clinical trial sponsors, principal investigators, and trial sites, and IRBs. If we or our CROs fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or other equivalent competent authorities in foreign jurisdictions may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that, upon inspection, the FDA or foreign regulatory authorities will determine that any of our clinical trials comply with GCPs. In addition, our clinical trials must be conducted with products produced under current Good Manufacturing Practices, or cGMPs and similar foreign requirements. Our failure or the failure of our CROs to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process and could also subject us to enforcement action up to and including civil and criminal penalties.

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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.

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

The COVID-19 pandemic has impacted multiple countries and regions, including the United States, Canada, Europe, and China, where we have planned or ongoing preclinical studies and clinical trials. If the COVID-19 pandemic and disruptions caused by government actions to limit its spread continue for a significant length of time, we may experience additional disruptions that could severely impact our business, preclinical studies, clinical trials and our commercialization prospects, including:

- delays in receiving approval from local regulatory authorities to initiate or conduct our planned clinical trials;
- further delays or difficulties in enrolling patients in our clinical trials;
- delays or difficulties in clinical site initiation, including difficulties in recruiting clinical site investigators and clinical site staff;
- further delays in clinical sites receiving the supplies and materials needed to conduct our clinical trials, including interruption in global shipping that may affect the transport of clinical trial materials;
- risk that participants enrolled in our clinical trials will contract COVID-19 while the clinical trial is ongoing, which could impact the results of the clinical trial, including by increasing the number of observed adverse events;
- interruptions or delays in preclinical studies due to restricted or limited operations at our contracted research and development laboratory facilities;
- interruptions or delays in manufacturing activities due to restricted or limited operations at our CMOs;
- delays in global shipping of raw materials, API, and/or finished goods between locations;
- interruptions or delays in delivery of clinical trial ancillary supplies, due to restricted or limited operations;
- continued limitations in employee resources that would otherwise be focused on the start-up or conduct of our clinical trials, including because of sickness of employees or their families or the desire of employees to avoid contact with large groups of people, or due to increased hiring and/or retention or other staffing issues;

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- refusal of the FDA or foreign regulatory authorities to accept data from clinical trials in affected geographies;
- impacts from prolonged remote work arrangements, such as increased cybersecurity risks and strains on our business continuity plans; and
- delays in the receipt of marketing authorizations for our product candidates, which could materially affect our commercialization plans.

As the COVID-19 pandemic continues to evolve, the extent to which the pandemic may further impact our business, preclinical studies, clinical trials and our commercialization prospects will depend on future developments, which are highly uncertain and cannot be predicted with confidence. While the potential economic impact brought by and the duration of the COVID-19 pandemic may be difficult to assess or predict, the widespread pandemic has resulted in, and may continue to result in, significant disruption of global financial markets, reducing our ability to access capital, which could in the future negatively affect our liquidity. In addition, the recession or economic downturn resulting from the spread of COVID-19 could materially affect our business.

Risks Related to the Commercialization of IMCIVREE (setmelanotide)

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

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

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

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

In some foreign countries, particularly in Canada, Great Britain and in the EU member states, the pricing and reimbursement of prescription only medicinal products is subject to strict governmental control which varies widely between countries. In these countries, pricing negotiations with governmental authorities can take six to twelve months or longer after the receipt of regulatory approval and product launch. To obtain favorable reimbursement for the indications sought or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost effectiveness of IMCIVREE with other available therapies. If reimbursement for IMCIVREE is unavailable in any country

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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

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

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

On December 13, 2021, Regulation No 2021/2282 on HTA, amending Directive 2011/24/EU, was adopted. While the Regulation entered into force in January 2022, it will only begin to apply from January 2025 onwards, with preparatory and implementation-related steps to take place in the interim. Once the Regulation becomes applicable, it will have a phased implementation depending on the concerned products. This regulation intends to boost cooperation among EU member states in assessing health technologies, including new medicinal products, and providing the basis for cooperation at the EU level for joint clinical assessments in these areas. The regulation foresees a three-year transitional period and will permit EU member states to use common HTA tools, methodologies, and procedures across the EU, working together in four main areas, including joint clinical assessment of the innovative health technologies with the most potential impact for patients, joint scientific consultations whereby developers can seek advice from HTA authorities, identification of emerging health technologies to identify promising technologies early, and continuing voluntary cooperation in other areas. Individual EU member states will continue to be responsible for assessing non-clinical (e.g., economic, social, ethical) aspects of health technology, and making decisions on pricing and reimbursement.

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

In order to market IMCIVREE, we must continue to build our sales, marketing, managerial and other non-technical capabilities or make arrangements with third parties to perform these services. Although we have received FDA approval, for IMCIVREE, for chronic weight management in adult EC and pediatric patients 6 years of age and older with obesity due to POMC, PCSK1 or LEPR deficiency, or BBS, from the EC UK MHRA marketing authorization to IMCIVREE, for the treatment of obesity and the control of hunger associated with genetically confirmed BBS or genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above, and for dosing in patients with POMC or LEPR deficiency who have mild, moderate or severe renal impairment, and MHRA authorization for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC, including

PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above, certain indications, we are early in our commercialization efforts and have not yet established a full-scale commercial infrastructure. Therefore, you should not compare us to commercial-stage biotechnology companies, and you should not expect that we will generate substantial revenues or become profitable in the near term. If we are unable to establish adequate sales, marketing and distribution capabilities,

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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.

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

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

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

The commercial success of IMCIVREE will also depend upon the awareness and acceptance of IMCIVREE within the medical community, including physicians, patients and third party payors. If IMCIVREE does not achieve an adequate level of acceptance by patients, physicians and third party payors, we may not generate sufficient revenue to become or remain

profitable. Before granting reimbursement approval, third party payors may require us to demonstrate that, in addition to treating obesity caused by certain genetic deficiencies affecting the MC4R pathway, IMCIVREE also provides incremental health benefits to patients. Our efforts to educate the medical community and third party payors about the benefits of IMCIVREE may require significant resources and may never be successful. All of these challenges may impact our ability to ever successfully market and sell IMCIVREE.

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

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

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- availability of alternative treatments, including a number of obesity therapies already approved or expected to be commercially launched in the near future;

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- our ability to increase awareness of these diseases among our target populations through marketing and other cross-functional efforts;
- the size of the target patient population, and the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the ability of IMCIVREE to treat the maximum range of pediatric patients, and any limitations on its indications for use;
- the strength of marketing and distribution support and timing of market introduction of competitive products;

- publicity concerning IMCIVREE or competing products and treatments;
- pricing and cost effectiveness;
- the effectiveness of our sales and marketing strategies;
- our ability to increase awareness of IMCIVREE through marketing efforts;
- our ability to obtain sufficient third-party coverage or reimbursement;
- the willingness of patients to pay out-of-pocket in the absence of third-party coverage; and
- the likelihood that competent authorities in foreign jurisdictions may require development of a REMS or other specific obligations as a condition of approval or post-approval, may not agree with our proposed REMS or other specific obligations, or may impose additional requirements that limit the promotion, advertising, distribution or sales of IMCIVREE.

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

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

Currently, IMCIVREE is the only approved treatment for providing chronic weight management in patients with obesity due to BBS or POMC, PCSK1 or LEPR deficiencies, and there are no approved treatments for chronic weight management in patients with Alström syndrome, or with deficiencies due to a variant in one of the two alleles in the *POMC, PCSK1, or LEPR* genes (HET obesity), SRC1 deficiency obesity, SH2B1 deficiency obesity, MC4R deficiency obesity, and hypothalamic obesity. Bariatric surgery is not a good treatment option for these genetic diseases of obesity because the severe obesity and hyperphagia associated with these diseases are considered to be risk factors for bariatric surgery. Also, existing therapies

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indicated for general obesity, including glucagon-like peptide-1 (GLP-1) receptor agonists, such as Wegovy®, and glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) agonists, such as tirzepatide which is being investigated as a treatment for obesity, do not specifically restore function

impaired by genetic deficiencies in the MC4R pathway, which we believe is the root cause of hyperphagia and obesity in patients with MC4R genetic variants. Based on search results from ClinicalTrials.gov, we are unaware of any competitive products in therapeutic clinical studies for the obesity and hyperphagia caused by upstream MC4R pathway deficiencies specifically, however LG Chem has represented it is in early-stage clinical development of an MC4R agonist. New competitors may emerge which could limit our business opportunity in the future.

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

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

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

We maintain product liability insurance coverage for our clinical trials and commercial product with a $10.0 $15.0 million annual aggregate coverage limit. Our insurance coverage may be insufficient to reimburse us for any expenses or losses we may suffer. Moreover, in the future, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses, including if insurance coverage becomes increasingly expensive. Large judgments have been awarded in class action lawsuits based on drugs that had unanticipated side effects. The cost of any product liability litigation or other proceedings, even if resolved in our favor, could be substantial, particularly in light of the size of our business and financial resources. A product liability claim or series of claims brought against us could cause our stock price to decline and, if we are unsuccessful in defending such a claim or claims and the resulting judgments exceed our insurance coverage, our financial condition, business and prospects could be materially adversely affected.

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

We do not currently have, nor do we plan to acquire, the infrastructure or capability to manufacture our clinical and commercial drug supply internally for setmelanotide, or any future product candidates, for use in the conduct of our

preclinical studies and clinical trials, and we lack the internal resources and the capability to manufacture any product candidate on a clinical or commercial scale. The facilities used by our contract manufacturing organizations, or CMOs, to manufacture the active pharmaceutical ingredient, or API, and final drug product must pass inspection by the FDA and other equivalent competent authorities in foreign jurisdictions pursuant to inspections that have been and will be conducted following submission of our NDAs or NDA supplements or relevant foreign regulatory submission submissions to the other equivalent competent authorities in foreign jurisdictions. Our failure or the failure of our CMOs to pass preapproval inspection of the manufacturing facilities of setmelanotide could delay the regulatory approval process. In addition, our clinical trials must be conducted with products produced under GMP and similar foreign regulations. Our failure or the failure of our CROs or CMOs to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process and could also subject us to enforcement action, including civil and criminal penalties. When we import any drugs or drug substances, we would be subject to FDA, United States Department of Agriculture, and U.S. Bureau of Customs and Border Patrol import regulation requirements. Such enforcement for our failure or our CROs or CMOs' failure to comply with these regulations could result in import delays, detention of products, and, depending on criteria such as the history of violative activities, the FDA could place a foreign firm or certain drug substances or products on Import Alert and require that all such drug substances or products be subject to detention without physical examination which could significantly impact the global supply chain for setmelanotide. With the exception of those on the FDA's drug shortage list or properly imported by individuals, the FDCA prohibits the importation of prescription drug products for commercial use if they were manufactured in a foreign country, unless they have been approved or are otherwise authorized to be marketed in the United States and are labeled accordingly.

We currently contract with third parties for the manufacture of setmelanotide and intend to continue to do so in the future. We have entered into process development and manufacturing service agreements with our CMOs, Corden Pharma Switzerland, LLC, or Corden, (formerly Peptisyntha SA prior to its acquisition by Corden), and Neuland Laboratories for certain process development and manufacturing services for regulatory starting materials and/or raw materials in connection with the manufacture of setmelanotide. We have entered into long-term commercial supply agreements with PolyPeptide Group and Recipharm Monts S.A.S. for manufacturing of drug substance and drug product for IMCIVREE. Under our agreements, we pay these third parties for services in accordance with the terms of mutually agreed upon work orders, which we may enter into from time to time. We may need to engage additional third party suppliers to manufacture our clinical and/or commercial (subject to approval) drug supplies. We also have engaged other third parties to assist in, among other things, distribution, post-approval safety reporting and pharmacovigilance activities. We cannot be certain that we can engage third party suppliers on terms as favorable as those that are currently in place.

We do not perform the manufacturing of any drug products and are completely dependent on our CMOs to comply with GMPs and similar foreign requirements for manufacture of both drug substance, or API and finished drug product. We recognize that we are ultimately responsible for ensuring that our drug substances and finished drug product are manufactured in accordance with GMPs and similar foreign requirements, and, therefore, the company's management practices and oversight, including routine auditing, are critical. If our CMOs cannot successfully manufacture material that conform to our specifications and the strict regulatory requirements of the FDA or other equivalent competent authorities in foreign jurisdictions, they may be subject to administrative and judicial enforcement for non-compliance and the drug products would be deemed misbranded or adulterated and prohibited from distribution into interstate commerce. Furthermore, all of our CMOs are engaged with other companies to supply and/or manufacture materials or products for such companies, which exposes our manufacturers to regulatory risks for the production of such materials and products. As a result, failure to satisfy the regulatory requirements for the production of those other company materials and products may affect the regulatory clearance of our CMOs' facilities generally. In addition, satisfying the regulatory requirements for production of setmelanotide with multiple suppliers, while assuring more robust drug availability in the future, adds additional complexity and risk to regulatory approval. If the FDA or another equivalent competent foreign regulatory agency does not approve these facilities for the manufacture of setmelanotide or if it withdraws its approval in the future,

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we may need to find alternative manufacturing facilities, which would adversely impact our ability to develop, obtain regulatory approval for or market setmelanotide.

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

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manufacturing of finished drug product could delay our planned clinical trials of setmelanotide and our commercial supply, which could delay, prevent or limit our ability to generate revenue and continue our business.

Moreover, as a result of the COVID-19 pandemic and ongoing global supply chain issues, certain of our suppliers and CMOs in Europe have been affected, which has disrupted their activities. As a result, we could face difficulty sourcing key components necessary to produce supply of setmelanotide, which may negatively affect our clinical development and commercialization activities. If the COVID-19 coronavirus further impacts business operations, including our CMOs and suppliers, we could face additional disruption to our supply chain that could affect the supply of drug product for preclinical, clinical trial and commercial use. Additionally, as our CMOs are producers of drug substances and drug products, including

vaccines and therapeutics, they could be compelled by a national government, or choose themselves, to shift their resources to the production of a COVID-19 vaccine and/or therapeutics for COVID-19, which could disrupt any scheduled drug substance or drug product batches we may have and may prevent us from obtaining supplies for our programs in a timely manner to meet our development timelines.

We do not have long term supply agreements in place with all of our contractors involved with the manufacturing of our weekly formulation of setmelanotide. We currently place individual batch or campaign orders with the CMOs/suppliers that are individually contracted under existing master services and quality agreements for the weekly formulation of setmelanotide. If we engage new contractors, we will be required to demonstrate comparability between product lots produced by such new contractors must be approved by and those we previously utilized, which could delay 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 development or commercialization of such products or product candidates. In addition, if manufacturing changes occur post-approval, the FDA and foreign regulatory authorities may have to approve these changes. changes before we are able to release product manufactured using revised processes. We plan to continue to rely upon CMOs and, potentially, collaboration partners to manufacture commercial quantities of setmelanotide. Our current scale of manufacturing appears adequate to support all of our current needs for clinical trial and initial commercial supplies for setmelanotide. Going forward, we may need to identify additional CMOs or partners to produce setmelanotide on a larger scale.

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

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

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

On October 28, 2022, we delivered a written notice to RareStone that we have terminated the RareStone License for cause. In accordance with the notice, we maintain that RareStone has materially breached its obligations under the RareStone License to fund, perform or seek certain key clinical studies and waivers, including with respect to the

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Company's global EMANATE trial, among other obligations. On December 21, 2022, RareStone has notified provided written notice to the Company that it objects to the claims in the Notice, our October 28, 2022 notice, including the Company's termination of the RareStone License for cause. On March 16, 2023, we provided written notice to RareStone reaffirming our position that RareStone has materially breached its obligations under the RareStone License and that we have terminated the RareStone License for cause, and that a formal response is forthcoming. also requested documentation supporting RareStone's purported dispute notice objecting to the claims in the Notice. RareStone may attempt to cure the alleged breaches, which we believe to be incurable, within the timeframe specified under the RareStone License. There can be no assurance that we will be able to negotiate an appropriate cure to the alleged material breaches and, if required, we expect to deliver a final termination notice upon seek appropriate relief under the expiration terms of the cure period specified in the RareStone License. Termination of, or any possible litigation focused on, the RareStone License could cause significant delays in our product development and commercialization efforts for setmelanotide and could prevent us from

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commercializing IMCIVREE in the markets covered by the RareStone License without first expanding our internal capabilities or entering into another agreement with a third party. Any alternative collaboration or license could also be on less favorable terms to us. In addition, under the agreement, RareStone agreed to provide funding for certain clinical development activities. To date, no such funding has been provided. If the agreement were terminated, however, we may need to refund any such potential payments and seek additional funding to support the research and development of setmelanotide or discontinue any research and development activities for setmelanotide in China, including mainland China, Hong Kong and Macao, which could have a material adverse effect on our business.

Risks Related to Our Intellectual Property Rights

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

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

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

Although an issued patent is presumed valid and enforceable, its issuance is not conclusive as to its validity or its enforceability and such patent may not provide us with adequate proprietary protection or competitive advantages against competitors with similar products. Patents, if issued, may be challenged, deemed unenforceable, invalidated or circumvented.

U.S. patents and patent applications or the patents and patent application obtained or submitted pursuant to comparable foreign laws, may also be subject to interference proceedings, *ex parte* reexamination, *inter partes* review proceedings, post-grant review proceedings, supplemental examination and challenges in court. Patents may be subjected to opposition or comparable proceedings lodged in various foreign, both national and regional, patent offices. These proceedings could result in either loss of the patent or denial of the patent application or loss or reduction in the scope of one or more of the claims of the patent or patent application. In addition, such proceedings may be costly. Thus, any patents that we may own or exclusively license may not provide any protection against competitors. Furthermore, an adverse decision in an interference proceeding can result in a third party receiving the patent right sought by us, which in turn could affect our ability to develop, market or otherwise commercialize setmelanotide.

Competitors may also be able to design around our patents. Other parties may develop and obtain patent protection for more effective technologies, designs or methods. The laws of some foreign countries do not protect our proprietary

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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

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parties covered setmelanotide, our financial position and results of operations would also be materially and adversely impacted.

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

- any of our patents, or any of our pending patent applications, if issued, will include claims having a scope sufficient to protect setmelanotide;
- any of our pending patent applications will issue as patents;
- we will be able to successfully commercialize IMCIVREE before our relevant patents expire;

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

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

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

Competitors may infringe our patents or the patents of our licensors. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming and divert the attention of our management and key personnel from our business operations. Even if we prevail in any lawsuits that we initiate, the damages or other remedies awarded may not be commercially meaningful. In addition, in an infringement proceeding,

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a court may decide that a patent of ours or our licensors is not valid, is unenforceable and/or is not infringed, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our patent applications at risk of not issuing.

Interference proceedings provoked by third parties or brought by us may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of

litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States.

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

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

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

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

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

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

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

- cease development of setmelanotide and commercialization of setmelanotide; IMCIVREE;
- pay substantial damages for past use of the asserted intellectual property;
- obtain a license from the holder of the asserted intellectual property, which license may not be available on reasonable terms, if at all; and

- in the case of trademark claims, rename setmelanotide and/or its trade name IMCIVREE.

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

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

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

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

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

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

Filing, prosecuting and defending patents on setmelanotide in all countries and jurisdictions throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States could be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third

parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our product and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents and other intellectual property protection, particularly those relating to biopharmaceuticals, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. For example, an April 2017 report from the Office of the United States Trade Representative identified a number of countries, including India and China, where challenges to the procurement and enforcement of patent rights have been reported. Several countries, including India and China, have been listed in the report every year since 1989. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial

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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

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the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

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

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

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

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

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

While we have received registered trademarks for the commercial trade name IMCIVREE (setmelanotide) and its logo in the United States, and the EU, and other countries, we have not yet obtained trademark protection for IMCIVREE in certain foreign jurisdictions and are pursuing trademark registrations in other jurisdictions. Our trademark applications may be rejected during trademark registration proceedings. Although we would be given an opportunity to respond to those rejections, we may be unable to overcome them. In addition, in the U.S. PTO and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive those proceedings.

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

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

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or restoration or the term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and our ability to generate revenues could be materially adversely affected.

Because setmelanotide contains active ingredients that the FDA has determined to be a new chemical entity, it has been afforded five years of marketing non-patent data exclusivity by the FDA. Following the expiration of this marketing exclusivity,

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

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

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

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

The United States has enacted and is currently implementing the America Invents Act of 2011, wide ranging patent reform legislation. Further, the U.S. Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain future patents, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the federal courts and the U.S. PTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents or future patents.

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

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

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

Even if we complete the necessary clinical trials, the regulatory and marketing approval process is expensive, time consuming and uncertain and may prevent us from obtaining additional approvals for the commercialization of setmelanotide beyond FDA approval for obesity due to POMC, PCSK1 or LEPR deficiencies, or BBS in the United

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States, for the treatment of obesity and the control of hunger associated with genetically confirmed BBS and confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above including patients with POMC or LEPR deficiency who have mild, moderate or severe renal impairment, and the MHRA marketing authorization for the treatment of obesity and the control of hunger associated with genetically confirmed BBS and confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. We depend primarily on the success of setmelanotide, and we cannot be certain that we will be able to obtain additional regulatory approvals for, or successfully commercialize, setmelanotide. If we are not able to obtain, or if there are delays in obtaining, required additional regulatory approvals, we will not be able to commercialize setmelanotide in additional indications in the United States or in foreign jurisdictions, and our ability to generate revenue will be materially impaired.

We currently have only one product candidate, setmelanotide, in clinical development, and our business depends entirely on its successful clinical development, regulatory approval and commercialization. In the United States, IMCIVREE is approved for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndromic obesity due to POMC, PCSK1 or LEPR deficiency as determined by a FDA-approved test demonstrating variants in *POMC*, *PCSK1* or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance, or BBS. The EC has authorized setmelanotide for the treatment of obesity and the control of hunger associated with genetically confirmed BBS or genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. The UK's MHRA authorized setmelanotide for the treatment of obesity and the control of hunger associated with genetically confirmed BBS or genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. Setmelanotide will require substantial additional clinical development, testing and regulatory approval before we are permitted to commence commercialization in indications beyond those currently approved for IMCIVREE in the United States, the EU and Great Britain. The clinical trials, manufacturing and marketing of setmelanotide are subject to extensive and rigorous review and regulation by numerous government authorities in the United States and in other countries where we intend to test and, if approved, market setmelanotide.

Before obtaining regulatory approvals for the commercial sale of any product candidate, we must demonstrate through nonclinical testing and clinical trials that the product candidate is safe and effective for use in each target indication. This process can take many years and approval, if any, may be conditional on postmarketing studies and surveillance, and will require the expenditure of substantial resources beyond our existing cash resources. Of the large number of drugs in development in the United States and in other countries, only a small percentage will successfully complete the FDA regulatory approval process or the equivalent process in foreign jurisdictions and will be commercialized. In addition, we have not discussed all of our proposed development programs with the FDA or the competent authorities of foreign jurisdictions. Accordingly, even if we are able to obtain the requisite financing to continue to fund our development and clinical trials, we cannot assure you that setmelanotide will be successfully developed or commercialized.

In addition, obtaining FDA approval of an NDA or NDA supplement for additional indications and the approval of an MAA or variation from the EC for additional indications is a complex, lengthy, expensive and uncertain process, and the FDA, EMA or equivalent competent authorities in foreign jurisdictions may delay, limit or deny approval of setmelanotide for many reasons, including, among others:

- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may disagree with our interpretation of data from clinical trials, or may change the requirements for approval even after it has reviewed and commented on the design for our clinical trials;

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- 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

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marketing approval. For example, the potential unblinding of setmelanotide studies due to easily identifiable AEs may raise the concern that potential bias has affected the clinical trial results;

- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may disagree with the number, size, conduct or implementation of our clinical trials;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may require that we conduct additional clinical trials or pre-clinical studies;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may not consider that our diagnostic strategy supports approval;

- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may decide that additional assays or data to understand any risks for anti-drug antibodies may need to be available for approval;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may decide that the toxicology program, including any parts of carcinogenicity studies that are filed, do not meet the requirements for approval;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions or the applicable foreign regulatory agency may identify deficiencies in our chemistry, manufacturing or controls of setmelanotide, or in the commercial production of setmelanotide to support product approval;
- the CROs that we retain to conduct our clinical trials may take actions outside of our control that materially adversely impact our clinical trials;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may find the data from preclinical studies and clinical trials insufficient to demonstrate that clinical and other benefits of setmelanotide outweigh its safety risks;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may disagree with our interpretation of data from our preclinical studies and clinical trials;
- the FDA the EMA, or other equivalent competent authorities in foreign jurisdictions may not approve the formulation, labeling or specifications of setmelanotide;
- the FDA, the EMA, or other equivalent competent authorities in foreign jurisdictions may not accept data generated at our clinical trial sites;
- the FDA, the EMA, or the equivalent competent authorities in foreign jurisdictions may require, as a condition of approval, additional preclinical studies or clinical trials, limitations on approved labeling or distribution and use restrictions;
- as part of our NDA approval, we were required to complete certain post-market requirements and commitments, which we may not be able to meet;

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- the FDA may require development of a REMS as a condition of additional approvals or may impose additional requirements that limit the promotion, advertising, distribution, or sales of setmelanotide;
- the EC may grant only conditional approval marketing authorization or based on the EMA's opinion impose specific obligations as a condition for marketing authorization, or may require us to conduct post authorization safety studies as a condition of grant of marketing authorization;

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

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

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

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

The EU pharmaceutical legislation is currently undergoing a complete review process, in the context of the Pharmaceutical Strategy for Europe initiative, launched by the EC in November 2020. A proposal for revision of several legislative instruments related to medicinal products (potentially revising the duration of regulatory exclusivity, eligibility for expedited pathways, etc.) is expected to be adopted by the EC by the end of during the first quarter or beginning of the second quarter half of 2023. The proposed revisions, once they are agreed and adopted by the European Parliament and European Council (not expected before the end of 2024 or early 2025), may have a significant impact on the pharmaceutical industry in the long term.

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

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

Separately, in response to the COVID-19 pandemic, in March 2020, the FDA announced its intention to postpone postponed most inspections of domestic and foreign manufacturing facilities and on March 18, 2020, at various points. Even though the FDA temporarily postponed routine surveillance inspections of domestic manufacturing facilities. Subsequently, in July 2020, the FDA resumed certain on-site inspections of domestic manufacturing facilities subject to a risk-based prioritization system. The FDA utilized this risk-based assessment system to assist in determining when and where it was safest to conduct prioritized domestic inspections. Additionally, on April 15, 2021, the FDA began conducting voluntary remote interactive evaluations of certain drug manufacturing facilities and clinical research sites, among other facilities in circumstances where the FDA determines

that such remote evaluation would be appropriate based on mission needs and travel limitations. In July 2021, the FDA has since resumed standard inspectional inspection operations of domestic facilities and was continuing to maintain this level of operation. More recently, where feasible, the FDA has continued to monitor and implement changes to its inspectional activities to ensure the safety of its employees and those of the firms it regulates as it adapts to the evolving COVID-19 pandemic. pandemic, and any resurgence of the virus or emergence of new variants may lead to further inspectional delays. Regulatory authorities outside the United States have adopted similar restrictions or other policy measures in response to the COVID-19 pandemic. If a prolonged government shutdown occurs, or if global health concerns continue to prevent the FDA or other regulatory authorities from conducting their regular inspections, reviews, or other regulatory activities, it could significantly impact the ability of the FDA or other regulatory authorities to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

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

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

Kingdom UK and/or the EU and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek marketing authorization in the United Kingdom UK and/or EU for any of our other product candidates, which could significantly and materially harm our business.

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

Regulatory authorities may impose significant restrictions on setmelanotide's indicated uses or marketing or impose ongoing requirements for potentially costly post approval studies. We and setmelanotide will also be subject to ongoing requirements by the FDA and foreign regulatory authorities, governing labeling, packaging, storage, advertising, promotion, marketing, distribution, importation, exportation, post-approval changes, manufacturing, recordkeeping, and submission of safety and other post market information. Advertising and promotional materials must comply with the FDCA and implementing regulations and foreign regulations, and are subject to FDA and foreign regulatory authorities oversight and post-marketing reporting obligations, in addition to other potentially applicable federal and state laws. The FDA and the other competent foreign authorities have significant post market authority, including, for example, the authority to require labeling changes based on new safety information and to require post market studies or clinical trials

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to evaluate serious safety risks related to the use of a drug. The FDA and foreign regulatory authorities also has the authority to require, as part of an NDA or similar foreign application or post approval, the submission of a REMS or other specific obligations, which may include Elements to Assure Safe Use. Any REMS or other specific obligations required by the FDA or foreign regulatory authorities may lead to increased costs to assure compliance with new post approval regulatory requirements and potential requirements or restrictions on the sale of approved products, all of which could lead to lower sales volume and revenue. The holder of an approved NDA also must submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process, or adding new manufacturers. Similar requirements apply in foreign jurisdictions.

Manufacturers of drug products and their facilities may be subject to payment of application and program fees and are subject to continual review and periodic inspections by the FDA and other equivalent competent authorities for

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compliance with cGMPs and other regulations. If we or a regulatory agency discover problems with setmelanotide, such as AEs of unanticipated severity or frequency, or problems with the facility where setmelanotide is manufactured or disagrees with the promotion, marketing or labeling of the product, a regulatory agency may impose restrictions on setmelanotide, the

manufacturer or us, including requiring withdrawal of setmelanotide from the market or suspension of manufacturing. If we or the manufacturing facilities for setmelanotide fail to comply with applicable regulatory requirements, a regulatory agency may, among other things:

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

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

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

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

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Similar to the United States, both marketing authorization holders and manufacturers of medicinal products are subject to comprehensive regulatory oversight by the EMA and the competent authorities of the individual EU member states, both before and after grant of the manufacturing and marketing authorizations. This oversight includes control of compliance with GMP rules, which govern quality control of the manufacturing process and require documentation policies and procedures. We and our third party manufacturers would be required to ensure that all of our processes, methods, and equipment are compliant with GMP. Failure by us or by any of our third party partners, including suppliers, manufacturers, and distributors to comply with EU laws and the related national laws of individual EU member states governing the conduct of clinical trials,

manufacturing approval, marketing authorization of medicinal products, both before and after grant of marketing authorization, and marketing of such products following grant of authorization may result in administrative, civil, or criminal penalties. These penalties could include delays in or refusal to authorize the conduct of clinical trials or to grant marketing authorization, product withdrawals and recalls, product seizures, suspension,

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revocation or variation of the marketing authorization, total or partial suspension of production, distribution, manufacturing, or clinical trials, operating restrictions, injunctions, suspension of licenses, fines, and criminal penalties.

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

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

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

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

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs, although this fee does not apply to sales of certain products approved exclusively for orphan indications;

- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;

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- expansion of manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs, revising the "average manufacturer price" definition, and extending rebate liability from fee-for-service Medicaid utilization to include the utilization of Medicaid managed care organizations as well as Medicaid managed care;

- expansion of the list of entity types eligible for participation in the Public Health Service 340B drug pricing program, or the 340B program, to include certain free-standing cancer hospitals, critical access hospitals, rural referral centers, and sole community hospitals, but exempting "orphan drugs," such as IMCIVREE, from the 340B ceiling price requirements for these covered entities;

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

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

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

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

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. For example, beginning April 1, 2013, Medicare payments to providers were reduced by 2% under the sequestration required by the Budget Control Act of 2011, which will remain in effect through 2030, 2032, unless additional Congressional action is taken. Under current legislation, the actual reduction in Medicare payments will increase in future years of the sequester. Additionally, on

January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Moreover, On March 11, 2021, the federal government and American Rescue Plan Act of 2021 was signed into law, which eliminates the individual states in the United States have become increasingly active in developing proposals, passing legislation and implementing regulations designed to control statutory Medicaid drug pricing, including rebate cap, currently set at 100% of a drug's average manufacturer price, or patient reimbursement constraints, discounts, formulary flexibility, marketing cost disclosure, drug price increase reporting, and other transparency measures. These types of initiatives may result in additional reductions in Medicare, Medicaid, and other healthcare funding, and may otherwise affect the prices we may obtain for IMCIVREE or the frequency with which IMCIVREE is prescribed or used. AMP, beginning January 1, 2024.

Additional changes that may affect our business include the expansion of new programs such as Medicare payment for performance initiatives for physicians under the Medicare Access and CHIP Reauthorization Act of 2015, or MACRA, which was fully implemented in 2019. At this time, it is unclear how the introduction of this Medicare quality payment program will impact overall physician reimbursement. The cost of prescription pharmaceuticals in the United States has also been the subject of considerable discussion in the United States. There have been several Congressional inquiries, as well as legislative and regulatory initiatives and executive orders designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products.

Table Moreover, the federal government and the individual states in the United States have become increasingly active in developing proposals, passing legislation and implementing regulations designed to control drug pricing, including price or patient reimbursement constraints, discounts, formulary flexibility, marketing cost disclosure, drug price increase reporting, and other transparency measures. These types of Contentsinitiatives may result in additional reductions in Medicare, Medicaid, and other healthcare funding, and may otherwise affect the prices we may obtain for IMCIVREE or the frequency with which IMCIVREE is prescribed or used.

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

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We expect that these and other healthcare reform measures that may be adopted in the future may result in more rigorous coverage and payment criteria and in additional downward pressure on the price that we receive for any approved drug. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our drugs. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our drug candidates or additional pricing pressures. We cannot predict with certainty what impact any federal or state health reforms will have on us, but such changes could impose new or more stringent regulatory requirements on our activities or result in reduced reimbursement for our products, any of which could adversely affect our business, results of operations and financial condition.

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

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

Medicaid is a joint federal and state program administered by the states for low income and disabled beneficiaries. We participate in and have certain price reporting obligations under the Medicaid Drug Rebate Program, or the MDRP, as a condition of having covered outpatient drugs payable under Medicaid and, if applicable, under Medicare Part B. The MDRP requires us to pay a rebate to state Medicaid programs every quarter for each unit of our covered outpatient drugs dispensed to Medicaid beneficiaries and paid for by a state Medicaid program. The rebate is based on pricing data that we must report on a monthly and quarterly basis to the Centers for Medicare & Medicaid Services, or CMS, the federal agency that administers the MDRP and other governmental healthcare programs. These data include the average manufacturer price (AMP) for each drug and, in the case of innovator products, the best price, which in general represents the lowest price available from the manufacturer to certain entities in the U.S. in any pricing structure, calculated to include all sales and associated rebates, discounts and other price concessions. The Medicaid rebate consists of two components, the basic rebate and the additional rebate, which is triggered if the AMP for a drug increases faster than inflation. If we become aware that our MDRP government price reporting submission for a prior quarter was incorrect or has changed as a result of recalculation of the pricing data, we must resubmit the corrected data for up to three years after those data originally were due. If we fail to provide information timely or are found to have knowingly submitted false information to the

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government, we may be subject to civil monetary penalties and other sanctions, including termination from the MDRP. In the event that CMS terminates our rebate agreement pursuant to which we participate in the MDRP, no federal payments would be available under Medicaid or Medicare Part B for our covered outpatient drugs. Our failure to comply with our MDRP price reporting and rebate payment obligations could negatively impact our financial results.

The ACA made significant changes to the MDRP, as described under the risk factor "*Current and future healthcare reform legislation or regulation may increase the difficulty and cost for us and any future collaborators to obtain marketing approval of and commercialize setmelanotide and may adversely affect the prices we, or they, may obtain and may have a negative impact on our business and results of operations*," above. In addition, in March 2021, the American Rescue Plan Act of 2021 was signed into law, which, among other things, eliminated the statutory cap on drug manufacturers' MDRP rebate liability, effective January 1, 2024. Under current law enacted as part of the ACA, drug

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manufacturers' MDRP rebate liability is capped at 100% of the average manufacturer price AMP for a covered outpatient drug. Congress could enact additional legislation that further increases Medicaid drug rebates or other costs and charges associated with participating in the MDRP. Additional legislation or the issuance of regulations relating to the MDRP could have a material adverse effect on our results of operations.

The recently-enacted IRA imposes rebates under Medicare Part B and Medicare Part D that are triggered by price increases that outpace inflation (first due in 2023), as described under the risk factor "*Current and future healthcare reform legislation or regulation may increase the difficulty and cost for us and any future collaborators to obtain marketing approval of and commercialize setmelanotide and may adversely affect the prices we, or they, may obtain and may have a negative impact on our business and results of operations*," above. The Medicare Part D rebate will be calculated on the basis of the AMP figures we report pursuant to the MDRP.

Federal law requires that any company that participates in the MDRP also participate in the Public Health Service's 340B drug pricing program in order for federal funds to be available for the manufacturer's drugs under Medicaid and, if applicable, Medicare Part B. We participate in the 340B program, which is administered by the Health Resources and Services Administration, or HRSA, and requires us to charge statutorily defined covered entities no more than the 340B "ceiling price" for our covered outpatient drugs. These 340B covered entities include a variety of community health clinics and other entities that receive health services grants from the Public Health Service, as well as hospitals that serve a disproportionate share of low-income patients. The ACA expanded the list of covered entities to include certain free-standing cancer hospitals, critical access hospitals, rural referral centers and sole community hospitals, but exempts "orphan drugs," such as IMCIVREE, from the ceiling price requirements for these covered entities. The 340B ceiling price is calculated using a statutory formula based on the average manufacturer price AMP and rebate amount for the covered outpatient drug as calculated under the MDRP, and in general, products subject to Medicaid price reporting and rebate liability are also subject to the 340B ceiling price calculation and discount requirement. We must report 340B ceiling prices to HRSA on a quarterly basis, and HRSA publishes those prices to 340B covered entities. In addition, HRSA has finalized regulations regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities for 340B-eligible drugs. HRSA has also finalized an administrative dispute resolution process through which 340B covered entities may pursue claims against participating manufacturers for overcharges, and through which manufacturers may pursue claims against 340B covered entities for engaging in unlawful diversion or duplicate discounting of 340B drugs. Our failure to comply

340B program requirements could negatively impact our financial results. Any additional future changes to the definition of average manufacturer price and the Medicaid rebate amount under the ACA or other legislation or regulation could affect our 340B ceiling price calculations and also negatively impact our financial results. In addition, legislation may be introduced that, if passed, would further expand the 340B program to additional covered entities or would require participating manufacturers to agree to provide 340B discounted pricing on drugs used in an inpatient setting.

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

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the VA on a quarterly and annual basis. Pursuant to applicable law, knowing provision of false information in connection with a Non-FAMP filing can subject a manufacturer to significant civil monetary penalties for each item of false information. The FSS pricing and contracting obligations also contain extensive disclosure and certification requirements.

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

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would be expensive and time-consuming, and could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

Individual states continue to consider and have enacted legislation to limit the growth of healthcare costs, including the cost of prescription drugs and combination products. A number of states have either implemented or are considering implementation of drug price transparency legislation. Requirements of pharmaceutical manufacturers under such laws include

advance notice of planned price increases, reporting price increase amounts and factors considered in taking such increases, wholesale acquisition cost information disclosure to prescribers, purchasers, and state agencies, and new product notice and reporting. Such legislation could limit the price or payment for certain drugs, and a number of states are authorized to impose civil monetary penalties or pursue other enforcement mechanisms against manufacturers who fail to comply with drug price transparency requirements, including the untimely, inaccurate, or incomplete reporting of drug pricing information.

Pricing and rebate calculations vary among products and programs. The calculations are complex and are often subject to interpretation by us, governmental or regulatory agencies, and the courts. CMS, the Department of Health & Human Services Office of Inspector General, and other governmental agencies have pursued manufacturers that were alleged to have failed to report these data to the government in a timely or accurate manner. Governmental agencies may also make changes in program interpretations, requirements or conditions of participation, some of which may have implications for amounts previously estimated or paid. We cannot assure you that any submissions we are required to make under the MDRP, the 340B program, the VA/FSS program, the Tricare Retail Pharmacy Program, and other governmental drug pricing programs will not be found to be incomplete or incorrect.

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

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

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

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other forms of obesity caused by defects in the MCR4 pathway. We are not currently permitted to, and do not, market or promote setmelanotide for these uses.

Regulatory authorities in the United States generally do not regulate the behavior of physicians in their choice of treatments. Regulatory authorities do, however, restrict communications by pharmaceutical companies on the subject of off-label use. Although recent court decisions suggest that certain off-label promotional activities may be protected under the First Amendment, the scope of any such protection is unclear. If our promotional activities fail to comply with the FDA's regulations or guidelines, we may be subject to warnings from, or enforcement action by, these authorities. In addition, our failure to follow

FDA rules and guidelines relating to promotion and advertising may cause the FDA to issue warning letters or untitled letters, bring an enforcement action against us, suspend or withdraw an approved product from the market, require a recall or institute fines or civil fines, or could result in disgorgement of money, operating restrictions, injunctions or criminal prosecution, any of which could harm our reputation and our business.

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

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

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

- The United States federal healthcare Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, or receiving remuneration, (anything of value), directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, lease order or arranging for or recommending the purchase, lease or order of any good or service for which payment may be made, in whole or in part, by federal healthcare programs such as Medicare and Medicaid. This statute has been interpreted to apply to arrangements between pharmaceutical companies on one hand and prescribers, purchasers, formulary managers, and patients on the other. Liability under the Anti-Kickback Statute may be established without proving actual knowledge of the statute or specific intent to violate it. Although there are a number of statutory exceptions and regulatory safe harbors to the federal Anti-Kickback Statute protecting certain common business arrangements and activities from prosecution or regulatory sanctions, the exceptions and safe harbors are drawn narrowly. Practices that involve remuneration to those who prescribe, purchase, or recommend pharmaceutical and biological products, including certain discounts, or engaging such individuals or patients as consultants, advisors, or speakers, may be subject to scrutiny if they do not fit squarely within an exception or safe harbor. Our practices may not in all cases meet all of the criteria for safe harbor protection from anti-kickback liability. Moreover, there are no safe harbors

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for many common practices, such as educational and research grants, charitable donations, product and patient support programs.

- The federal civil False Claims Act prohibits individuals or entities from, among other things, knowingly presenting, or causing to be presented a false or fraudulent claim for payment of government funds, or knowingly making, using or causing to made or used a false record or statement material to an obligation to pay money to the government or knowingly concealing or knowingly and improperly avoiding, decreasing or concealing an obligation to pay money to the federal government. Actions under the False Claims Act may be brought by the Attorney General or as a qui tam action by a private individual in the name of the government. Such private individuals may share in amounts paid by the entity to the government in recovery or settlement. Many pharmaceutical manufacturers have been investigated and have reached substantial financial settlements with the federal government under the civil False Claims Act for a variety of alleged improper activities including causing false claims to be submitted as a result of the marketing of their products for unapproved and thus non-reimbursable uses, inflating prices reported to private price publication

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services which are used to set drug payment rates under government healthcare programs, and other interactions with prescribers and other customers including those that may have affected their billing or coding practices and submission to the federal government. The government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. False Claims Act liability is potentially significant in the healthcare industry because the statute provides for treble damages and significant mandatory penalties per false or fraudulent claim or statement for violations. Because of the potential for large monetary exposure, healthcare and pharmaceutical companies often resolve allegations without admissions of liability for significant and material amounts to avoid the uncertainty of treble damages and per claim penalties that may be awarded in litigation proceedings. Settlements may require companies to enter into corporate integrity agreements with the government, which may impose substantial costs on companies to ensure compliance. Pharmaceutical and other healthcare companies also are subject to other federal false claims laws, including, among others, federal criminal healthcare fraud and false statement statutes that extend to non-government health benefit programs.

- The federal Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program, including private third-party payors, and also imposes obligations, with respect to safeguarding the privacy, security and transmission of individually identifiable health information. Penalties for failure to comply with a requirement of HIPAA vary significantly and include civil monetary penalties as well as criminal penalties for knowingly obtaining or disclosing individually identifiable health information in violation of HIPAA. The criminal penalties increase if the wrongful conduct involves false pretenses or the intent to sell, transfer or use identifiable health information for commercial advantage, personal gain or malicious harm. HIPAA also prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement or representation, or making or using any false writing or document knowing the same to contain any materially false, fictitious or fraudulent statement or entry in connection with the delivery of or payment for healthcare benefits, items or services. Similar to the federal healthcare Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it to have committed a violation.

- The federal Physician Payments Sunshine Act, implemented as the Open Payments Program, requires certain manufacturers of drugs, devices, biologics and medical supplies to report payments and other transfers of value to physicians for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report annually to the United States Department of Health and Human Services, Centers for Medicare and Medicaid Services, information related to physicians (defined to include doctors, dentists, optometrists, podiatrists, and chiropractors), certain non-physician practitioners (physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, anesthesiology assistants and certified nurse-midwives) and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Manufacturers must submit

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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.

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

Ensuring that our business arrangements and interactions with healthcare professionals, third party payors, patients and others comply with applicable healthcare laws and regulations will require substantial resources. Various state, federal and foreign regulatory and enforcement agencies continue actively to investigate violations of health care laws and regulations, and the United States Congress continues to strengthen the arsenal of enforcement tools.

It is possible that governmental authorities will conclude that our business practices do not comply with current or future statutes, regulations or case law involving applicable fraud and abuse, privacy, or other healthcare laws and regulations. If our operations, including our engagements with healthcare professionals, researchers and patients, or our disease awareness and/or patient identification initiatives including genetic testing programs, or anticipated activities to be conducted by our field teams, were found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to costly investigations, significant civil, criminal and administrative monetary penalties, imprisonment, damages, fines, disgorgement, exclusion from government funded healthcare programs, such as Medicare and Medicaid, contractual damages, diminished profits and future earnings, and the curtailment or restructuring of our operations, any of which could substantially disrupt our operations or financial results. Although compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. Any action against us for violation of these laws or regulations, even if we successfully defend against it, could cause us to incur significant legal expenses and generate negative publicity, which could harm our financial condition and divert our management's attention from the operation of our business.

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

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with the regulations of the FDA and applicable non U.S. regulators, provide accurate information to the FDA and applicable non U.S. regulators, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee misconduct could also involve the improper use of, including trading on, information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter employee misconduct, and any precautions

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we take to detect and prevent this activity may be ineffective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws

or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions. Some of these laws and related risks are described under the risk factor "*We may be subject to federal and state healthcare laws and regulations. If we are unable to comply or have not fully complied with such laws and regulations, we could face criminal sanctions, damages, substantial civil penalties, reputational harm and diminished profits and future earnings*" of this Annual Report.

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

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

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

In the United States, numerous federal and state laws and regulations, including HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 and regulations implemented thereunder, collectively HIPAA, state data breach notification laws, state health information privacy laws and federal and state consumer protection laws, including Section 5 of the Federal Trade Commission Act, which govern the collection, use, disclosure and protection of health-related and other personal information, may apply to our operations and the operations of current and future collaborators. We may obtain health information from third parties, such as research institutions with which we collaborate, that are subject to privacy and security requirements under HIPAA. Although we are not directly subject to HIPAA, other than potentially with respect to providing certain employee benefits, we could be subject to criminal penalties if we knowingly obtain or disclose individually identifiable health information maintained by a HIPAA covered entity in a manner that is not authorized or permitted by HIPAA. In addition, state laws govern the privacy and security of health, research and genetic information in specified circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. Further, we may also be subject to other state laws governing the privacy, processing and protection of personal information. For example, the California Consumer Privacy Act of 2018, or CCPA, went into effect on January 1, 2020. The CCPA creates individual privacy rights for California consumers and increases the privacy and security obligations of entities handling certain personal information. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that is expected to increase has increased the likelihood, and risks associated with data breach litigation. Further, the California Privacy Rights Act, or CPRA, recently passed in California. The CPRA will impose generally went into effect on January 1, 2023, and significantly amends the CCPA. It imposes additional data protection obligations on covered businesses, including additional consumer rights processes, limitations on data uses, new audit requirements for

higher risk data, and opt outs for certain uses of sensitive data. It will also create creates a new California data protection agency authorized to issue substantive regulations and could result in increased privacy and information security enforcement. The majority of the provisions will go into effect on January 1, 2023, and additional Additional compliance investment and potential business process changes may also be required. Similar laws have passed in Virginia, Utah, Iowa, Connecticut and Colorado, and have been proposed in other states and at the federal level, reflecting a trend toward more stringent privacy legislation in the United States. The enactment of such laws could have potentially conflicting requirements that would make compliance challenging. In addition, some of our research activities involve minors, which may be subject to additional laws and can require specialized consent processes, privacy protections, and compliance procedures. In the event that we are subject to or affected by HIPAA, the CCPA, the CPRA or other domestic privacy and data protection laws, any liability from failure to comply with the requirements of these laws could adversely affect our financial condition.

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

Our operations abroad may also be subject to increased scrutiny or attention from data protection authorities. For example, in Europe, the collection and use of personal data, including health and genetic data, is governed by the provisions of the GDPR. The GDPR became effective on May 25, 2018, and imposes strict requirements for the processing of the personal data of individuals within the European Economic Area, or EEA, or in the context of our activities in the EEA, including health data from clinical trials and AE reporting. In particular, these requirements include certain obligations

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concerning the consent of the individuals to whom the personal data relates, the information provided to the individuals, the transfer of personal data out of the EU, the EEA, and the United Kingdom, security breach notifications, and security and confidentiality of the personal data, and violations of these requirements could result in substantial fines, up to the greater of 20 million Euros or 4% of total global annual turnover. In addition to the foregoing, a breach of the GDPR could result in regulatory investigations, reputational damage, orders to cease/change our processing of our data, enforcement notices, and/or assessment notices for a compulsory audit. We may also face civil claims including representative actions and other class action type litigation (where individuals have suffered harm), potentially amounting to significant compensation or damages

liabilities, as well as associated costs, diversion of internal resources, and reputational harm. Data protection authorities from the different EU and EEA member states may also interpret the GDPR and national laws differently and impose additional requirements, which adds to the complexity of processing personal data in the EU and the EEA.

Additionally, from January 1, 2021, we have had to comply with the GDPR and also the United Kingdom GDPR, or UK GDPR, which, together with the amended United Kingdom Data Protection Act 2018, retains the GDPR in United Kingdom national law following Brexit. The UK GDPR mirrors the fines under the GDPR, e.g. fines up to the greater of €20 million (£17.5 million) or 4% of global turnover. The relationship between the United Kingdom and the EU in relation to certain aspects of data protection law remains unclear, and it is unclear how United Kingdom data protection laws and regulations will develop in the medium to longer term.

Among other requirements, the GDPR and UK GDPR also regulate transfers of personal data subject to the GDPR or UK GDPR to third countries that have not been found to provide adequate protection to such personal data, including the United States; in July, 2020, the Court of Justice of the European Union, or the CJEU, invalidated the EU-US Privacy Shield Framework, or the Privacy Shield, under which personal data could be transferred from the EEA to US entities who had self-certified under the Privacy Shield scheme and imposed further restrictions on the use of the standard contractual clauses, or SCCs. These restrictions include a requirement for companies to carry out a transfer impact assessment which, among other things, assesses the laws governing access to personal data in the recipient country and considers whether supplementary measures that provide privacy protections additional to those provided under SCCs will need to be implemented to ensure an essentially equivalent level of data protection to that afforded in the EEA. The EC issued revised SCCs In March 2022, the US and EU announced a new regulatory regime intended to replace the invalidated regulations; however, this new EU-US Data Privacy Framework has not been implemented beyond an executive order signed by President Biden on June 4, 2021 to account October 7, 2022 on Enhancing Safeguards for the decision of the CJEU and recommendations made by the European Data Protection Board. The revised SCCs must be used for relevant new data transfers from September 27, 2021; existing standard contractual clauses arrangements must be migrated to the revised clauses by December 27, 2022. There is some uncertainty around whether the revised clauses can be used for all types of data transfers, particularly whether they can be relied on for data transfers to non-EEA entities subject to the GDPR. The revised SCCs apply only to the transfer of personal data outside of the EEA and not the United Kingdom. The United Kingdom's Information Commissioner's Office has also published new data transfer standard contracts for transfers from the UK under the UK GDPR. This new documentation will be mandatory for relevant data transfers from September 21, 2022; existing standard contractual clauses arrangements must be migrated to the new documentation by March 21, 2024. We will be required to implement the latest UK data transfer documentation for data transfers subject to the UK GDPR, in relation to relevant existing contracts and certain additional contracts and vendor/customer arrangements, within the relevant time frames. States Signals Intelligence Activities. As supervisory authorities issue further guidance on personal data export mechanisms, including circumstances where the standard contractual clauses cannot be used, and/or start taking enforcement action, we could suffer additional costs, complaints and/or regulatory investigations or fines, and/or if we are otherwise unable to transfer personal data between and among countries and regions

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in which we operate, it could affect the manner in which we provide our services, the geographical location or segregation of our relevant systems and operations, and could adversely affect our financial results. The EC has adopted an adequacy decision in favor of the United Kingdom, enabling data transfers from EU member states to the United Kingdom without additional safeguards. However, the UK adequacy decision will automatically expire in June 2025 unless the EC re-assesses and renews/extends that decision, and remains under review by the EC during this period. The relationship between the United

Kingdom and the EU in relation to certain aspects of data protection law remains unclear, and it is unclear how United Kingdom data protection laws and regulations will develop in the medium to longer term, and how data transfers to and from the United Kingdom will be regulated in the long term. In September 2021, the UK government launched a consultation on its proposals for wide-ranging reform of UK data protection laws following Brexit and the response to this consultation was published in June 2022. There is a risk that any material changes which are made to the UK data protection regime could result in the EC reviewing the UK adequacy decision, and the UK losing its adequacy decision if the EC deems the UK to no longer provide adequate protection for personal data.

The EU has also proposed a Regulation on Privacy and Electronic Communications, or ePrivacy Regulation, which, if adopted, would impose new obligations on the use of personal data in the context of electronic communications, particularly with respect to online tracking technologies and direct marketing. Additionally, the EU adopted the EU Clinical Trials Regulation, which came into effect on January 31, 2022. This regulation imposes new obligations on the use of data generated from clinical trials and enables European patients to have the opportunity to access information about clinical trials.

Although we work to comply with applicable laws, regulations and standards, our contractual obligations and other legal obligations, these requirements are evolving and may be modified, interpreted and applied in an inconsistent manner from one jurisdiction to another, and may conflict with one another or other legal obligations with which we must comply. Our failure to comply with our obligations under the GDPR or UK GDPR, including any failure to adopt measures to ensure that we can continue to conduct the data processing activities that we initiated in the EU before the GDPR entered into application, the UK GDPR, the ePrivacy Regulation, the EU Clinical Trials Regulations, and other countries' privacy or data security-related laws could adversely impact our ability to use the data generated in our studies. And any actual or perceived failure to comply with these data protection laws or adequately address privacy and security concerns could lead to government enforcement actions and significant penalties against us, and adversely impact our operating results.

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

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

- our customers' ability to obtain reimbursement for setmelanotide in foreign markets;
- our inability to directly control commercial activities because we are relying on third parties;

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- 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;

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- reduced protection of intellectual property rights in some foreign countries;
- foreign currency exchange rate fluctuations; and
- the interpretation of contractual provisions governed by foreign laws in the event of a contract dispute.

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

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

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

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

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

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

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

Following a national referendum and enactment of legislation by the government of the United Kingdom, UK, the United Kingdom UK formally withdrew from the EU on January 31, 2020 and ratified a trade and cooperation agreement governing its future relationship (commonly referred to as "Brexit"). The agreement, which was applied provisionally from January 1, 2021 and entered into force on May 1, 2021, addresses trade, economic arrangements, law enforcement, judicial cooperation and a governance framework including procedures for dispute resolution, among other things. Because

Since the agreement merely sets forth a framework in many respects and will require complex additional bilateral negotiations between the United Kingdom and the EU as both parties continue to work on the rules for implementation, significant political and economic uncertainty remains about how the precise terms end of the relationship between Brexit transition period on January 1, 2021, the parties will differ from the terms before withdrawal.

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Since January 1, 2021, however, the United Kingdom operates UK has operated under a separate regulatory regime to the EU. EU laws regarding medicinal products only apply in respect of the United Kingdom UK to Northern Ireland (as set out in the Protocol on Ireland/Northern Ireland). However, under the Retained EU Law (Revocation and Reform) Bill 2022, which is currently before the UK parliament, any retained EU law not expressly preserved and "assimilated" into domestic law or extended by ministerial regulations (to no later than June 23, 2026) will automatically expire and be revoked by December 31, 2023. The EU laws that have been transposed into United Kingdom law through secondary legislation remain applicable. While the United Kingdom UK has indicated a general intention that new laws regarding the development, manufacture and commercialization of medicinal products in the United Kingdom UK will align closely with EU law, there are remain limited detailed proposals for future regulation of medicinal products. The trade and cooperation agreement includes specific provisions concerning medicinal products, which include the mutual recognition of GMP, inspections of manufacturing facilities for medicinal products and GMP documents issued (such mutual recognition can be rejected by either party in certain circumstances), but does not foresee wholesale mutual recognition of United Kingdom UK and EU pharmaceutical regulations. For example, despite the UK carrying out a public consultation on future changes to the clinical trials legislation, which ended on March 14, 2022, new UK legislation has not yet been published and so it is not clear still somewhat uncertain as to what extent whether the United Kingdom UK clinical trials requirements will adopt legislation aligned align with or similar to, the EU CTR which became applicable in the EU on January 31, 2022 and which significantly reforms the assessment and supervision processes for clinical trials throughout the EU. Therefore, there remains political and economic uncertainty regarding to what extent the regulation of medicinal products will differ between the United Kingdom UK and the EU in the future. Any divergences will increase the cost and complexity of running our business, including with respect to the conduct of clinical trials. Brexit also materially impacted the regulatory regime with respect to the approval of our product candidates. Great Britain is no longer covered by the EU's procedures for the grant of marketing authorizations (Northern Ireland is covered by the centralized authorization procedure and can be covered under the decentralized or mutual recognition procedures). As of January 1, 2021, all existing centralized marketing authorizations were automatically converted into United Kingdom UK marketing authorizations effective in Great Britain and issued with a United Kingdom UK marketing authorization number on January 1,

2021 (unless marketing authorization holders opted out of this scheme). A separate marketing authorization is now required to market drugs in Great Britain. It is currently unclear whether the regulator in the United Kingdom, UK, the MHRA is sufficiently prepared to handle the increased volume of marketing authorization applications that it is likely to receive. Any delay in obtaining, or an inability to obtain, any regulatory approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in Great Britain and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in Great Britain for our product candidates, which could significantly and materially harm our business. The United Kingdom's UK's withdrawal from the EU and the associated uncertainty has had and may continue to have a significant adverse effect on global economic conditions and the stability of global financial markets, and could significantly reduce global market liquidity and restrict the ability of key market participants to operate in certain financial markets. Asset valuations, currency exchange rates and credit ratings may be especially subject to increased market volatility. Any of these factors could have a significant adverse effect on our business, financial condition, results of operations and prospects.

Risks Related to the Acquisition of Xinvento B.V.

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

In February 2023, in order to expand our pipeline and build on our focus on rare endocrinology diseases, we acquired Xinvento B.V., a Netherlands-based biotech company focused on developing therapies for congenital hyperinsulinism (CHI). We expect that the integration process will be complex, costly and time-consuming. As a result, we are devoting, and will continue to be required to devote, significant management attention and resources to integrating Xinvento B.V. into our business. The integration process may be disruptive to our business and the expected benefits may not be achieved within the anticipated time frame, or at all. The Xinvento B.V. intellectual property may not have the

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scientific value and commercial potential which we envision. We may not be able to integrate the two businesses successfully, and we could assume unknown or contingent liabilities. It is possible that the integration process could result in the diversion of our management's attention, the disruption or interruption of, or the loss of momentum in, our ongoing business or inconsistencies in standards, controls, procedures and policies, any of which could adversely affect our ability to maintain relationships with third parties or the ability to achieve the anticipated benefits of the acquisition of Xinvento B.V., or could otherwise adversely affect our business and financial results.

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

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

Risks Related to Employee Matters and Managing Growth

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

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

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

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

The physical expansion of our operations may lead to significant costs and may divert financial resources from other projects, such as the development of setmelanotide. Many of our suppliers and collaborative and clinical trial relationships are located outside the United States, and we may in the future seek to hire employees located outside of the United States. Accordingly, our business may become subject to economic, political, regulatory and other risks associated with international operations, such as compliance with tax, employment, immigration and labor laws for employees living or traveling abroad, workforce uncertainty in countries where labor unrest is more common than in the United States, as well as difficulties associated with staffing and managing international operations, including differing labor relations. Any

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of these factors could materially affect our business, financial condition and results of operations. Our future financial performance and our ability to commercialize setmelanotide, if approved, and compete effectively will depend, in part, on our ability to effectively manage the future development and expansion of our company.

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

In the ordinary course of our business, we collect and store sensitive data, including intellectual property, our proprietary business information and that of our suppliers, as well as personally identifiable information of employees. Similarly, our third-party CROs, CMOs and other contractors and consultants possess certain of our sensitive data. The secure maintenance of this information is material to our operations and business strategy. Despite the implementation of security measures, our internal computer information technology systems and those of our third-party CROs, CMOs and other contractors and consultants are vulnerable to attack, damage, or interruption by hacking, cyberattacks, computer viruses and malware (e.g. ransomware), malicious code, phishing attacks and other social engineering schemes, unauthorized access, natural disasters, terrorism, telecommunication and electrical failures, employee theft or misuse, human error, fraud, denial or degradation of service attacks, sophisticated nation-state and nation-state-supported actors or unauthorized access or use by persons inside our organization, or persons with access to systems inside our organization. Any such attack, incident or breach could compromise our information technology systems and the information stored there could be accessed, publicly disclosed, lost, corrupted or stolen. Further, attacks upon information technology systems are increasing in their frequency, levels of persistence, sophistication and intensity, and are being conducted by sophisticated and organized groups and individuals with a wide range of motives and expertise. As a result of the COVID-19 pandemic, we may also face increased cybersecurity risks due to our reliance on internet technology and the number of our employees who are working remotely, which may create additional opportunities for cybercriminals to exploit vulnerabilities. Because the techniques used to obtain unauthorized access to, or to sabotage, systems change frequently and often are not recognized until launched against a target, we may be unable to anticipate these techniques or implement adequate preventative measures. We may also experience security breaches that may remain undetected for an extended period. Even if identified, we may be unable to adequately investigate or remediate incidents or breaches due to attackers increasingly using tools and techniques that are designed to circumvent controls, to avoid detection, and to remove or obfuscate forensic evidence.

The legislative and regulatory landscape for privacy and data protection continues to evolve, and there has been an increasing amount of focus on privacy and data protection issues with the potential to affect our business, including

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recently enacted laws in a majority of states requiring security breach notification, some also require implementation of reasonable security measures and provide a private right of action in the event of a breach. Costs of breach response, mitigation, investigation, remediation, notice and ongoing assessments can be considerable. Thus, any access, disclosure, damage or other loss of information, including our data being breached at our partners or third-party providers, could result in legal claims or proceedings and liability under state, federal and international privacy laws, disruption of our operations, and damage to our reputation, which could adversely affect our business.

We and certain of our service providers have been and from time to time will continue to be subject to cyberattacks and security incidents. While we do not believe that we have experienced any significant system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our programs. For example, the loss of clinical trial data for setmelanotide or other product candidates could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of or damage to our data or applications or other data or applications relating to our technology or product candidates, or inappropriate disclosure of confidential or proprietary information, we could incur liabilities and the further development of setmelanotide and our product candidates could be delayed. It could also expose us to risks, including an inability to provide our services and fulfill contractual demands, and could cause management distraction and the obligation to devote significant financial and other resources to mitigate such problems, which would increase our future information security costs, including through organizational changes, deploying additional personnel, reinforcing administrative, physical and technical safeguards, further training of employees, changing third-party vendor control practices and engaging third-party subject matter experts and consultants and reduce the demand for our product and services. We maintain cyber liability insurance; however, this insurance may

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not be sufficient to cover the financial, legal, business or reputational losses that may result from an interruption or breach of our systems.

Risks Related to Our Common Stock

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

Our executive officers and directors and their respective affiliates, in the aggregate, hold shares representing approximately 10.8% 5.5% of our outstanding voting stock as of September 30, 2022 March 31, 2023. 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.

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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 EC to approve IMCIVREE for additional indications;
- announcements of new products, technologies, commercial relationships, acquisitions or other events by us or our competitors;
- the success or failure of other weight loss therapies and companies targeting rare diseases and orphan drug treatment;
- regulatory or legal developments in the United States and other countries;
- failure of setmelanotide, if approved, to achieve commercial success;

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- 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;

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- our execution of any collaborative, licensing or similar arrangements, and the timing of payments we may make or receive under these arrangements;
- the achievement and timing of milestone payments under our existing collaboration and license agreements; and
- if setmelanotide receives regulatory approval, the level of underlying demand for that product and customers' buying patterns.

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

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

Under the Code, a corporation is generally allowed a deduction for net operating losses, or NOLs, carried over from a prior taxable year, and can use such NOLs to offset future taxable income, if any, until such losses are used or, for NOLs arising in taxable years ending on or before December 31, 2017, until such NOLs expire. Other unused tax attributes,

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such as research tax credits may also be carried forward to offset future taxable income, if any, until such attributes are used or expire. As of December 31, 2021 December 31, 2022, we had approximately $422.3 million $494.5 million and $385.1 $484.6 million of unused federal and state NOL carryforwards, respectively, and approximately $9.3 million $11.6 million and $4.2 $3.6 million of unused federal and state carryforwards of research tax credits, respectively. Of the federal NOL carryforwards at December 31, 2021 December 31, 2022, $349.2 million $421.3 million can be carried forward indefinitely, while $73.2 million will begin to expire in 2033. Additionally, as of December 31, 2021 December 31, 2022, we had federal orphan drug credits related to qualifying research of $15.4 million $19.3 million.

If a corporation undergoes an "ownership change," very generally defined as a greater than 50% change by value in its equity ownership by certain shareholders or groups of shareholders over a rolling three-year period, Sections 382 and 383 of the Code limit the corporation's ability to use carryovers of its pre-change NOLs, credits and certain other tax attributes to reduce its tax liability for periods after the ownership change. Our issuance of common stock pursuant to prior public offerings may have resulted in a limitation under Code Sections 382 and 383, either separately or in combination with certain prior or subsequent shifts in the ownership of our common stock. Future changes in our stock ownership, some of which are outside of our control, could also result in an ownership change under Sections 382 and 383 of the Code. In addition, for taxable years beginning after December 31, 2020, utilization of federal NOLs generated in tax years beginning after December 31, 2017 are limited to a maximum of 80% of the taxable income for such year, after taking into account utilization of NOLs generated in years beginning before January 1, 2018 and determined without regard to such NOL deduction. Further regulatory changes could also limited our ability to utilize our NOLs. As a result, our ability to use carryovers of NOLs and credits to reduce our future U.S. federal income tax liability may be subject to limitations. This could result in increased U.S. federal income tax liability for us if we generate taxable income in a future period. Limitations on the use of NOLs and other tax attributes could also increase our state tax liability. Any such limitation could have a material adverse effect on our results of operations in future years. We have not completed a study to assess whether an ownership change for purposes of Section 382 or 383 has occurred, or whether there have been multiple ownership changes since our inception, due to the significant costs and complexities associated with such study.

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

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

Sales of our common stock in the public market, or the perception that these sales could occur, could cause the market price of our common stock to decline significantly. As of September 30, 2022 March 31, 2023, we had 55,756,256 56,852,404 shares of common stock outstanding.

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The holders of an aggregate of approximately 6.0 million 3.1 million shares of our common stock, or approximately 10.8% 5.5% of our total outstanding common stock as of September 30, 2022 March 31, 2023, are entitled to rights with respect to the registration of their shares under the Securities Act, subject to specified conditions, until such shares can otherwise be sold without restriction under Rule 144 or until the rights terminate pursuant to the terms of the investors' rights agreement between us and such holders. We have also registered and intend to continue to register all shares of common stock that we

may issue under our equity compensation plans. Once we register these shares under the Securities Act, the shares become freely tradable without restriction under the Securities Act, except for shares purchased by affiliates and those subject to lock-up agreements, if applicable. As of November 8, 2022, approximately 175,000 shares of our common stock held by our executive officers are subject to restrictions on transfer under lock-up agreements with the underwriters of our recent follow-on offering. Specifically, we and our executive officers have agreed, subject to certain exceptions, not to offer, sell, contract to sell, pledge or otherwise dispose of, directly or indirectly, any of our common stock or securities convertible into or exchangeable or exercisable for any of our common stock, enter into a transaction that would have the same effect, or enter into any swap or other arrangement that transfers, in whole or in part, any of the economic consequences of ownership of our common stock, whether any of these transactions are to be settled by delivery of our common stock or other securities, in cash or otherwise, or publicly disclose the intention to make any offer, sale, pledge or disposition, or to enter into any transaction, swap, hedge or other arrangement, for 90 days after September 14, 2022 without first obtaining the written consent of Cowen and Company, LLC, who may release any of the securities subject to these lock-up agreements at any time without notice. Any sales of securities by these stockholders could have a material adverse effect on the trading price of our common stock.

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

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

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

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

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

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

- establish a classified board of directors so that not all members of our board are elected at one time;
- permit only the board of directors to establish the number of directors and fill vacancies on the board;
- provide that directors may only be removed "for cause" and only with the approval of two-thirds of our stockholders;

- authorize the issuance of "blank check" preferred stock that our board could use to implement a stockholder rights plan (also known as a "poison pill");

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- 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.

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

Our certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for: (i) any derivative action or proceeding brought on our behalf; (ii) any action asserting a claim of breach of fiduciary duty; (iii) any action asserting a claim against us arising under the DGCL, our certificate of incorporation or our bylaws; and (iv) any action asserting a claim against us that is governed by the internal affairs doctrine. In addition, our bylaws provide that the federal

district courts of the United States are the exclusive forum for any complaint raising a cause of action arising under the Securities Act. Any person or entity purchasing or otherwise acquiring any interest in any of our securities shall be deemed to have notice of and consented to the provisions of our certificate of incorporation and bylaws described above. These exclusive-forum provisions may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage lawsuits against us and our directors, officers and other employees. If a court were to find these provisions of our certificate of incorporation or bylaws to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving the dispute in other jurisdictions, which could seriously harm our business.

General Risk Factors

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

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

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or prevent us from realizing their expected benefits or enhancing our business. We cannot assure you that, following any such acquisition, we will achieve the expected synergies to justify the transaction.

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

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

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

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

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

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

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

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets. For example, the recent The global economy, including credit and financial crisis markets, has caused recently experienced extreme volatility and disruptions, in the capital including severely diminished liquidity and credit markets. availability, rising interest and inflation rates, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. A severe or prolonged economic downturn or recession and a continued increase in inflation rates or interest rates could result in a variety of risks to our business, including weakened demand for setmelanotide and our ability to raise additional capital when needed on acceptable terms, if at all. There can be no assurance that further deterioration in credit and financial markets and confidence in economic conditions will not occur. A weak or declining economy could also strain our suppliers, possibly resulting in supply disruption, or cause our customers to delay making payments for our services. Increased inflation rates and related increases in interest rates can adversely affect us by increasing our costs, including labor and employee benefit costs. In addition, the current military conflict between Russia and Ukraine could disrupt or otherwise adversely impact our operations and those of third parties upon which we rely. Related sanctions, export controls or other actions have and may in the future be initiated by nations including the U.S., the EU or Russia (e.g., potential cyberattacks, disruption of energy flows, etc.), which could adversely affect our business and/or our supply chain, our CROs, CMOs and other third parties with which we conduct business. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business.

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We have incurred and will continue to incur substantial costs as a result of operating as a public company, our management will continue to devote substantial time to new compliance initiatives and corporation governance policies,

and we will need to hire additional qualified accounting and financial personnel with appropriate public company experience.

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

These rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory

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and governing bodies. This could result in future uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

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

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

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

In addition, because once we no longer qualify as an emerging growth company, a non-accelerated filer or, if before such date, we are opt to no longer take advantage of the applicable exemption, we will again be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. If we are unable to maintain effective internal control over financial reporting, we may not have adequate, accurate or timely financial information, our independent registered public accounting firm may issue a report that is adverse, and we may be unable to meet our reporting obligations as a public company or comply with the requirements of the SEC or Section 404. This could result in a restatement of our financial statements, the imposition of sanctions, including the inability of registered broker dealers to make a market in our common stock, or investigation by regulatory authorities. Any such action or other negative results caused by our inability to meet our reporting requirements or comply with legal and regulatory requirements or by disclosure of an accounting, reporting or control issue could adversely affect the trading price of our securities and our business. Material weaknesses in our internal control over financial reporting could also

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reduce our ability to obtain financing or could increase the cost of any financing we obtain. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

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

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

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

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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.

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Item 6. Exhibits

Exhibit Number	Exhibit Description	Incorporated by Reference		
		Form	Date	Number
3.1	Amended and Restated Certificate of Incorporation.	10-Q	05/04/2020	3.1
3.2	Amended and Restated Bylaws.	8-K	12/11/2020	3.1
31.1*	Certification of the Principal Executive Officer, as required by Section 302 of the Sarbanes-Oxley Act of 2002 (18 U.S.C. 1350).			
31.2*	Certification of the Principal Financial Officer, as required by Section 302 of the Sarbanes-Oxley Act of 2002 (18 U.S.C. 1350).			
32.1**	Certification of the Principal Executive Officer, as required by Section 906 of the Sarbanes-Oxley Act of 2002 (18 U.S.C. 1350).			
32.2**	Certification of the Principal Financial Officer, as required by Section 906 of the Sarbanes-Oxley Act of 2002 (18 U.S.C. 1350).			

101.INS*	Inline XBRL Instance Document - the Instance Document does not appear in the interactive data file because its XBRL tags are embedded within the Inline XBRL document.	
101.SCH*	Inline XBRL Taxonomy Extension Schema Document.	
101.CAL*	Inline XBRL Taxonomy Extension Calculation Linkbase Document.	
101.DEF*	Inline XBRL Taxonomy Extension Definition Linkbase Document.	
101.LAB*	Inline XBRL Taxonomy Extension Label Linkbase Document.	
101.PRE*	Inline XBRL Taxonomy Extension Presentation Linkbase Document.	
104*	Cover Page Interactive Data File (formatted as Inline XBRL and contained in Exhibit 101).	

		Incorporated by Reference		
Exhibit Number	Exhibit Description	Form	Date	Number
2.2	Share Purchase Agreement, by and between Rhythm Pharmaceuticals Netherlands B.V. and Xinvento B.V., dated February 27, 2023.	10-K	03/01/2023	2.2
3.1	Amended and Restated Certificate of Incorporation.	10-Q	05/04/2020	3.1
3.2	Amended and Restated Bylaws.	8-K	12/11/2020	3.1
10.2	Summary of Non-Employee Director Compensation Policy.	10-K	03/01/2023	10.6
31.1*	Certification of the Principal Executive Officer, as required by Section 302 of the Sarbanes-Oxley Act of 2002 (18 U.S.C. 1350).			
31.2*	Certification of the Principal Financial Officer, as required by Section 302 of the Sarbanes-Oxley Act of 2002 (18 U.S.C. 1350).			
32.1**	Certification of the Principal Executive Officer, as required by Section 906 of the Sarbanes-Oxley Act of 2002 (18 U.S.C. 1350).			
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101.LAB*	Inline XBRL Taxonomy Extension Label Linkbase Document.
101.PRE*	Inline XBRL Taxonomy Extension Presentation Linkbase Document.
104*	Cover Page Interactive Data File (formatted as Inline XBRL and contained in Exhibit 101).

* Filed herewith.

** Furnished herewith.

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SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

RHYTHM PHARMACEUTICALS, INC.

Dated: November 8, 2022 May 2, 2023

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

Dated: November 8, 2022 May 2, 2023

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

Exhibit 31.1

CERTIFICATION

I, David P. Meeker, certify that:

1. I have reviewed this quarterly report on Form 10-Q of Rhythm Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: November 8, 2022 May 2, 2023

/s/ David P. Meeker, M.D.

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

Exhibit 31.2

CERTIFICATION

I, Hunter C. Smith, certify that:

1. I have reviewed this quarterly report on Form 10-Q of Rhythm Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: November 8, 2022 May 2, 2023

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

Exhibit 32.1

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

I, David P. Meeker, M.D., certify pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to the best of my knowledge, the Quarterly Report on Form 10-Q of Rhythm Pharmaceuticals, Inc. for the fiscal quarter ended September 30, 2022 March 31, 2023 (the "Report") fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, and the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of Rhythm Pharmaceuticals, Inc.

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

November 8, 2022 May 2, 2023

Exhibit 32.2

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

I, Hunter C. Smith, certify pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to the best of my knowledge, the Quarterly Report on Form 10-Q of Rhythm Pharmaceuticals, Inc. for the fiscal quarter ended September 30, 2022 March 31, 2023 (the "Report") fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934 and the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of Rhythm Pharmaceuticals Inc.

/s/ Hunter C. Smith

Name: Hunter C. Smith

Title: Chief Financial Officer and Treasurer

(*Principal Financial Officer*)

Novermber 8, 2022 May 2, 2023

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