

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-Q

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

For the quarterly period ended March 31, 2024

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 001-36407

ALNYLAM PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware
(State or Other Jurisdiction of
Incorporation or Organization)

675 West Kendall Street,
Henri A. Termeer Square
Cambridge, MA
(Address of Principal Executive Offices)

77-0602661
(I.R.S. Employer
Identification No.)

02142
(Zip Code)

(617) 551-8200
(Registrant's Telephone Number, Including Area Code)

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, \$0.01 par value per share	ALNY	The Nasdaq Stock Market LLC

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

At April 26, 2024, the registrant had 126,491,778 shares of Common Stock, \$0.01 par value per share, outstanding.

**ALNYLAM PHARMACEUTICALS, INC.
QUARTERLY REPORT ON FORM 10-Q**

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“Alnylam,” ONPATTRO[®], AMVUTTRA[®], GIVLAARI[®], OXLUMO[®], Alnylam Act[®] and IKARIA[™] are trademarks and registered trademarks of Alnylam Pharmaceuticals, Inc. Our logo, trademarks and service marks are property of Alnylam. All other trademarks or service marks appearing in this Quarterly Report on Form 10-Q are the property of their respective holders.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Quarterly Report on Form 10-Q contains forward-looking statements within the meaning of the federal securities laws, Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. We intend these forward-looking statements to be covered by the safe harbor provisions for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995 and are including this statement for purposes of complying with those safe harbor provisions. All statements other than statements of historical facts contained in this Quarterly Report on Form 10-Q are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as “may,” “will,” “should,” “could,” “expects,” “plans,” “intends,” “anticipates,” “believes,” “estimates,” “predicts,” “potential,” “continue,” or the negative of these terms or other comparable terminology. These forward-looking statements include, but are not limited to, statements about:

- our views with respect to the potential for approved and investigational RNAi therapeutics, including ONPATTRO, AMVUTTRA, GIVLAARI, OXLUMO, Leqvio® (inclisiran), fitusiran and zilebesiran;
- our plans for additional global regulatory filings and the continuing product launches of ONPATTRO, AMVUTTRA, GIVLAARI, OXLUMO and our collaborator’s plans with respect to Leqvio;
- the potential results of the HELIOS-B Phase 3 clinical trial of vutrisiran and our future ability to obtain regulatory approval of AMVUTTRA (vutrisiran) for the treatment of ATTR amyloidosis with cardiomyopathy;
- our expectations regarding potential market size for, and the successful commercialization of, ONPATTRO, AMVUTTRA, GIVLAARI, OXLUMO, Leqvio or any future products;
- our ability to obtain and maintain regulatory approvals and pricing and reimbursement for ONPATTRO, AMVUTTRA, GIVLAARI, OXLUMO or any future products, and our collaborators’ ability with respect to Leqvio and fitusiran;
- the progress of our research and development programs, including programs in both rare and prevalent diseases;
- the potential for improved product profiles to emerge from our new technologies, including our IKARIA platform and our ability to expand our product engine to include extrahepatic tissues;
- our current and anticipated clinical trials and expectations regarding the reporting of data from these trials;
- the timing of regulatory filings and interactions with, or actions or advice of, regulatory authorities, which may affect the design, initiation, timing, continuation and/or progress of clinical trials, or result in the need for additional pre-clinical and/or clinical testing or the timing or likelihood of regulatory approvals;
- the status of our manufacturing operations and any delays, interruptions or failures in the manufacture and supply of ONPATTRO, AMVUTTRA, GIVLAARI, OXLUMO or any of our product candidates (or other products or product candidates being developed and commercialized by our collaborators), by our or their contract manufacturers or by us or our collaborators;
- the impact of any future pandemics or public health emergencies on, among other things, our financial performance, business and operations, including manufacturing, supply chain, research and development activities and pipeline programs, and other potential impacts to our business;
- any impact of the on-going conflicts in Ukraine and the Middle East, including disruptions to our clinical trials;
- our progress continuing to build and leverage global commercial infrastructure;
- the possible impact of any competing products on the commercial success of ONPATTRO, AMVUTTRA, GIVLAARI, OXLUMO and Leqvio, as well as our product candidates, and, our, or with respect to Leqvio or fitusiran, our collaborators’, ability to compete against such products;
- our ability to manage our growth and operating expenses;
- our views and plans with respect to our 5-year *Alynlam P⁵x25* strategy and our intentions to achieve the metrics associated with this strategy, including to become a top-tier biotech company by the end of 2025, and our ability to successfully execute on our *Alynlam P⁵x25* strategy;
- our belief that our current cash balance should enable us to achieve a self-sustainable profile without the need for future equity financing;
- our expectations regarding the length of time our current cash, cash equivalents and marketable equity and debt securities will support our operations based on our current operating plan;
- our dependence on third parties for development, manufacture and distribution of products;

- our expectations regarding our corporate collaborations, including potential future licensing fees and milestone and royalty payments under existing or future agreements;
- our ability to obtain, maintain and protect our intellectual property;
- our ability to attract and retain qualified key management and scientists, development, medical and commercial staff, consultants and advisors;
- the outcome of litigation, including our patent infringement suits against Pfizer, Inc., BioNTech SE and Moderna, Inc., or of other legal proceedings or government investigations;
- regulatory developments in the United States, or U.S., and foreign countries;
- the impact of laws and regulations;
- developments relating to our competitors and our industry;
- our ability to satisfy our payment obligations, and to service the interest on, or to refinance our indebtedness, including our convertible notes, or to make cash payments in connection with any conversion of our convertible notes, to the extent required; and
- our expectations regarding the effect of the capped call transactions and the anticipated market activities of the option counterparties and/or their respective affiliates.

The risks set forth above are not exhaustive. Other sections of this Quarterly Report on Form 10-Q may include additional factors that could adversely affect our business and financial performance. Moreover, we operate in a very competitive and rapidly changing environment. New risk factors emerge from time to time and it is not possible for management to predict all risk factors, nor can we assess the impact of all risk factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements. Any forward-looking statements in this Quarterly Report on Form 10-Q reflect our current views with respect to future events and with respect to our business and future financial performance, and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by these forward-looking statements. Factors that may cause actual results to differ materially from current expectations include, among other things, those described under Part II, Item 1A, "Risk Factors" and elsewhere in this Quarterly Report on Form 10-Q. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future. You are advised, however, to consult any further disclosure we make in our reports filed with the Securities and Exchange Commission, or SEC.

PART I. FINANCIAL INFORMATION
ITEM 1. FINANCIAL STATEMENTS (Unaudited)

ALNYLAM PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED BALANCE SHEETS
(In thousands, except per share amounts)
(Unaudited)

	March 31, 2024	December 31, 2023
ASSETS		
Current assets:		
Cash and cash equivalents	\$ 681,879	\$ 812,688
Marketable debt securities	1,678,147	1,615,516
Marketable equity securities	11,256	11,178
Accounts receivable, net	321,377	327,787
Inventory	93,988	89,146
Prepaid expenses and other current assets	201,960	126,382
Total current assets	2,988,607	2,982,697
Property, plant and equipment, net	523,460	526,057
Operating lease right-of-use assets	195,468	199,732
Restricted investments	49,390	49,391
Other assets	67,461	72,003
Total assets	<u>\$ 3,824,386</u>	<u>\$ 3,829,880</u>
LIABILITIES AND STOCKHOLDERS' DEFICIT		
Current liabilities:		
Accounts payable	\$ 78,148	\$ 55,519
Accrued expenses	698,865	713,013
Operating lease liability	41,672	41,510
Deferred revenue	76,850	102,753
Liability related to the sale of future royalties	46,174	54,991
Total current liabilities	941,709	967,786
Operating lease liability, net of current portion	237,829	243,101
Deferred revenue, net of current portion	185,506	188,175
Convertible debt	1,021,732	1,020,776
Liability related to the sale of future royalties, net of current portion	1,336,892	1,322,248
Other liabilities	319,990	308,438
Total liabilities	4,043,658	4,050,524
Commitments and contingencies (Note 13)		
Stockholders' deficit:		
Preferred stock, \$0.01 par value per share, 5,000 shares authorized and no shares issued and outstanding as of March 31, 2024 and December 31, 2023	—	—
Common stock, \$0.01 par value per share, 250,000 shares authorized; 126,463 shares issued and outstanding as of March 31, 2024; 125,794 shares issued and outstanding as of December 31, 2023	1,265	1,259
Additional paid-in capital	6,881,977	6,811,063
Accumulated other comprehensive loss	(26,988)	(23,375)
Accumulated deficit	(7,075,526)	(7,009,591)
Total stockholders' deficit	(219,272)	(220,644)
Total liabilities and stockholders' deficit	<u>\$ 3,824,386</u>	<u>\$ 3,829,880</u>

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

ALNYLAM PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF OPERATIONS
AND COMPREHENSIVE LOSS
(In thousands, except per share amounts)
(Unaudited)

	Three Months Ended March 31,	
	2024	2023
Statements of Operations		
Revenues:		
Net product revenues	\$ 365,163	\$ 276,328
Net revenues from collaborations	118,548	36,462
Royalty revenue	10,622	6,500
Total revenues	494,333	319,290
Operating costs and expenses:		
Cost of goods sold	54,613	41,432
Cost of collaborations and royalties	11,363	13,437
Research and development	260,995	230,569
Selling, general and administrative	210,797	183,659
Total operating costs and expenses	537,768	469,097
Loss from operations	(43,435)	(149,807)
Other (expense) income:		
Interest expense	(35,253)	(28,955)
Interest income	29,645	18,655
Other expense, net	(14,544)	(12,255)
Total other expense, net	(20,152)	(22,555)
Loss before income taxes	(63,587)	(172,362)
Provision for income taxes	(2,348)	(1,739)
Net loss	<u>\$ (65,935)</u>	<u>\$ (174,101)</u>
Net loss per common share - basic and diluted	<u>\$ (0.52)</u>	<u>\$ (1.40)</u>
Weighted-average common shares used to compute basic and diluted net loss per common share	<u>126,138</u>	<u>124,111</u>
Statements of Comprehensive Loss		
Net loss	\$ (65,935)	\$ (174,101)
Other comprehensive (loss) income:		
Unrealized (loss) gain on marketable securities	(3,568)	4,125
Foreign currency translation (loss) gain	(78)	1,410
Defined benefit pension plans, net of tax	33	(5)
Total other comprehensive (loss) income	<u>(3,613)</u>	<u>5,530</u>
Comprehensive loss	<u>\$ (69,548)</u>	<u>\$ (168,571)</u>

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

ALNYLAM PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF STOCKHOLDERS' DEFICIT
(In thousands)
(Unaudited)

	Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Stockholders' Deficit
	Shares	Amount				
Balance as of December 31, 2023	125,794	\$ 1,259	\$ 6,811,063	\$ (23,375)	\$ (7,009,591)	\$ (220,644)
Exercise of common stock options, net of tax withholdings	223	2	24,763	—	—	24,765
Issuance of common stock under equity plans	446	4	(4)	—	—	—
Stock-based compensation charges	—	—	46,155	—	—	46,155
Other comprehensive loss	—	—	—	(3,613)	—	(3,613)
Net loss	—	—	—	—	(65,935)	(65,935)
Balance as of March 31, 2024	<u>126,463</u>	<u>\$ 1,265</u>	<u>\$ 6,881,977</u>	<u>\$ (26,988)</u>	<u>\$ (7,075,526)</u>	<u>\$ (219,272)</u>

	Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Stockholders' Deficit
	Shares	Amount				
Balance as of December 31, 2022	123,925	\$ 1,240	\$ 6,454,540	\$ (44,654)	\$ (6,569,349)	\$ (158,223)
Exercise of common stock options, net of tax withholdings	269	3	26,415	—	—	26,418
Issuance of common stock under equity plans	47	—	—	—	—	—
Stock-based compensation charges	—	—	41,136	—	—	41,136
Other comprehensive income	—	—	—	5,530	—	5,530
Net loss	—	—	—	—	(174,101)	(174,101)
Balance as of March 31, 2023	<u>124,241</u>	<u>\$ 1,243</u>	<u>\$ 6,522,091</u>	<u>\$ (39,124)</u>	<u>\$ (6,743,450)</u>	<u>\$ (259,240)</u>

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

ALNYLAM PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)
(Unaudited)

	Three Months Ended March 31,	
	2024	2023
Cash flows from operating activities:		
Net loss	\$ (65,935)	\$ (174,101)
Non-cash adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	13,517	14,065
Amortization and interest accretion related to operating leases	11,969	12,014
Non-cash interest expense on liability related to the sale of future royalties	31,565	25,275
Stock-based compensation expense	45,347	39,947
Realized and unrealized (gain) loss on marketable equity securities	(78)	2,267
Change in fair value of development derivative liability	8,586	6,471
Other	(5,188)	(6,276)
Changes in operating assets and liabilities:		
Accounts receivable, net	410	19,153
Inventory	22	(403)
Prepaid expenses and other assets	(75,462)	(1,235)
Accounts payable, accrued expenses and other liabilities	(4,865)	(81,975)
Operating lease liability	(12,840)	(12,827)
Deferred revenue	(28,563)	(8,850)
Net cash used in operating activities	<u>(81,515)</u>	<u>(166,475)</u>
Cash flows from investing activities:		
Purchases of property, plant and equipment	(12,973)	(13,891)
Purchases of marketable securities	(420,115)	(435,746)
Sales and maturities of marketable securities	365,468	373,420
Proceeds from maturity of restricted investments	39,975	49,225
Purchases of restricted investments	(39,975)	(49,225)
Net cash used in investing activities	<u>(67,620)</u>	<u>(76,217)</u>
Cash flows from financing activities:		
Proceeds from exercise of stock options and other types of equity, net	25,859	42,371
Proceeds from development derivative, net	3,052	4,000
Net cash provided by financing activities	<u>28,911</u>	<u>46,371</u>
Effect of exchange rate changes on cash, cash equivalents and restricted cash	(9,941)	2,176
Net decrease in cash, cash equivalents and restricted cash	(130,165)	(194,145)
Cash, cash equivalents and restricted cash, beginning of period	814,884	868,556
Cash, cash equivalents and restricted cash, end of period	<u>\$ 684,719</u>	<u>\$ 674,411</u>
Supplemental disclosure of cash flows:		
Cash paid for interest	\$ 30,945	\$ 13,912

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

ALNYLAM PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
(Unaudited)

1. NATURE OF BUSINESS

Alnylam Pharmaceuticals, Inc. (also referred to as Alnylam, the Company, we, our or us) commenced operations on June 14, 2002 as a biopharmaceutical company seeking to develop and commercialize novel therapeutics based on ribonucleic acid interference, or RNAi. We are committed to the advancement of our company strategy of building a multi-product, global, commercial biopharmaceutical company with a deep and sustainable clinical pipeline of RNAi therapeutics for future growth and a robust, organic research engine for sustainable innovation and great potential for patient impact. Since inception, we have focused on discovering, developing and commercializing RNAi therapeutics by establishing and maintaining a strong intellectual property position in the RNAi field, establishing strategic collaborations with leading pharmaceutical and life sciences companies, generating revenues through licensing agreements, and ultimately developing and commercializing RNAi therapeutics globally, either independently or with our strategic collaborators. We have devoted substantially all of our efforts to business planning, research, development, manufacturing and commercial efforts, acquiring, filing and expanding intellectual property rights, recruiting management and technical staff, and raising capital.

In early 2021, we launched our *Alnylam P⁵x25* strategy, which focuses on our planned transition to a top-tier biotech company by the end of 2025. With *Alnylam P⁵x25*, we aim to deliver transformative rare and prevalent disease medicines for patients around the world through sustainable innovation, while delivering exceptional financial performance.

As of March 31, 2024, we have five marketed products, including one collaborated product, and multiple late-stage investigational programs advancing towards potential commercialization. We currently generate worldwide product revenues from four commercialized products, ONPATTRO, AMVUTTRA, GIVLAARI and OXLUMO, primarily in the United States, or U.S., and Europe.

2. BASIS OF PRESENTATION AND PRINCIPLES OF CONSOLIDATION

The accompanying condensed consolidated financial statements of Alnylam are unaudited and have been prepared in accordance with accounting principles generally accepted in the United States of America, or GAAP, applicable to interim periods and, in the opinion of management, include all normal and recurring adjustments that are necessary to state fairly the results of operations for the reported periods. Our condensed consolidated financial statements have also been prepared on a basis substantially consistent with, and should be read in conjunction with, our audited consolidated financial statements for the year ended December 31, 2023, which were included in our Annual Report on Form 10-K that was filed with the Securities and Exchange Commission on February 15, 2024. The year-end condensed consolidated balance sheet data was derived from our audited financial statements but does not include all disclosures required by GAAP. The results of our operations for any interim period are not necessarily indicative of the results of our operations for any other interim period or for a full fiscal year.

The accompanying condensed consolidated financial statements reflect the operations of Alnylam and our wholly-owned subsidiaries. All intercompany accounts and transactions have been eliminated.

Our significant accounting policies are described in Note 2 of the Notes to Consolidated Financial Statements included in our Annual Report on Form 10-K for the year ended December 31, 2023.

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 assets and liabilities at the date of the condensed consolidated financial statements and the reported amounts of revenues and expenses during the reporting period. In our condensed consolidated financial statements, we use estimates and assumptions related to our inventory valuation and related reserves, liability related to the sale of future royalties, development derivative liability, income taxes, deferred tax asset valuation allowances, revenue recognition, research and development expenses, and stock-based compensation. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable. Actual results could differ from those estimates. Changes in estimates are reflected in reported results in the period in which they become known.

Liquidity

Based on our current operating plan, we believe that our cash, cash equivalents and marketable securities as of March 31, 2024 will be sufficient to satisfy our working capital and operating needs for at least the next 12 months from the filing date of this Quarterly Report on Form 10-Q.

Recent Accounting Pronouncements

In December 2023, the Financial Accounting Standards Board, or FASB, issued Accounting Standards Update 2023-09, Improvements to Income Tax Disclosures, which requires entities to disclose disaggregated information about their effective

ALNYLAM PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
(Unaudited)

tax rate reconciliation as well as expanded information on income taxes paid by jurisdiction. The disclosure requirements will be applied on a prospective basis, with the option to apply them retrospectively. The standard is effective for fiscal years beginning after December 15, 2024, with early adoption permitted. We are currently evaluating the disclosure requirements related to this new standard.

In November 2023, the FASB issued Accounting Standards Update 2023-07, Segment Reporting (Topic 280): Improvements to Reportable Segment Disclosures, which is intended to improve reportable segment disclosure requirements, primarily through additional disclosures about significant segment expenses. The standard is effective for fiscal years beginning after December 15, 2023, and interim periods within fiscal years beginning after December 15, 2024, with early adoption permitted. The amendments should be applied retrospectively to all prior periods presented in the financial statements. We are currently evaluating the disclosure requirements related to this new standard.

3. NET PRODUCT REVENUES

Net product revenues, classified based on the geographic region in which the product is sold, consist of the following:

(In thousands)	Three Months Ended March 31,	
	2024	2023
ONPATTRO		
United States	\$ 16,539	\$ 29,817
Europe	44,690	59,678
Rest of World	7,988	12,998
Total	<u>69,217</u>	<u>102,493</u>
AMVUTTRA		
United States	130,238	79,013
Europe	43,733	6,768
Rest of World	21,270	15,987
Total	<u>195,241</u>	<u>101,768</u>
GIVLAARI		
United States	38,731	30,291
Europe	15,315	14,471
Rest of World	4,010	3,144
Total	<u>58,056</u>	<u>47,906</u>
OXLUMO		
United States	13,332	9,057
Europe	21,427	13,309
Rest of World	7,890	1,795
Total	<u>42,649</u>	<u>24,161</u>
Total net product revenues	<u>\$ 365,163</u>	<u>\$ 276,328</u>

The following table presents the balance of our receivables related to our net product revenues:

(In thousands)	As of March 31, 2024	As of December 31, 2023
Receivables included in "Accounts receivable, net"	\$ 239,975	\$ 210,097

ALNYLAM PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
(Unaudited)

4. NET REVENUES FROM COLLABORATIONS

Net revenues from collaborations consist of the following:

(In thousands)	Three Months Ended March 31,	
	2024	2023
Roche	\$ 74,680	\$ —
Regeneron Pharmaceuticals	26,764	19,990
Novartis AG	14,516	14,933
Other	2,588	1,539
Total	\$ 118,548	\$ 36,462

The following table presents the balance of our receivables, contract assets and contract liabilities related to our collaboration agreements:

(In thousands)	As of March 31, 2024	As of December 31, 2023
Receivables included in "Accounts receivable, net"	\$ 66,344	\$ 99,576
Contract assets included in "Prepaid expenses and other current assets"	\$ 65,000	\$ —
Contract liabilities included in "Deferred revenue"	\$ 262,248	\$ 290,763

We recognized revenue of \$20.4 million and \$15.4 million in the three months ended March 31, 2024 and 2023, respectively, that was included in the contract liability balance at the beginning of the period.

To determine revenue recognized in the period from contract liabilities, we first allocate revenue to the individual contract liability balance outstanding at the beginning of the period until the revenue exceeds that balance. If additional consideration is received on those contracts in subsequent periods, we assume all revenue recognized in the reporting period first applies to the beginning contract liability as opposed to a portion applying to the new consideration for the period.

The following table provides research and development expenses incurred by type, for which we recognize net revenue, that are directly attributable to our collaboration agreements, by collaborator:

(In thousands)	Three Months Ended March 31,					
	2024			2023		
	Clinical and Manufacturing	External Services	Other	Clinical and Manufacturing	External Services	Other
Roche	\$ 14,135	\$ 3,612	\$ 334	\$ —	\$ —	\$ —
Regeneron Pharmaceuticals	10,789	3,741	4,173	8,516	1,240	9,363
Other	2,106	—	707	312	126	360
Total	\$ 27,030	\$ 7,353	\$ 5,214	\$ 8,828	\$ 1,366	\$ 9,723

The research and development expenses incurred for the agreements included in the table above consist of costs incurred for (i) clinical and preclinical expenses, including manufacturing of clinical and preclinical product, (ii) external services including consulting services and lab supplies and services, and (iii) other expenses, including professional services, facilities and overhead allocations, and a reasonable estimate of compensation and related costs as billed to our counterparties, for which we recognize net revenues from collaborations. For the three months ended March 31, 2024 and 2023, we did not incur material selling, general and administrative expenses related to our collaboration agreements.

Product Collaborations

Roche

On July 21, 2023, or the Effective Date, we entered into a Collaboration and License Agreement, or the Roche Agreement, with F. Hoffmann-La Roche Ltd. and Genentech, Inc., or collectively, Roche, pursuant to which we and Roche established a worldwide, strategic collaboration for the joint development of zilebesiran. Zilebesiran is our investigational small interfering RNA, or siRNA, therapeutic targeting liver-expressed angiotensinogen, which is currently in Phase 2 clinical development for the treatment of hypertension.

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Under the Roche Agreement, we granted to Roche (i) co-exclusive rights to develop zilebesiran worldwide and commercialize zilebesiran in the U.S., referred to as the Co-Commercialization Territory, (ii) exclusive rights to commercialize zilebesiran outside of the U.S., referred to as the Roche Territory, and (iii) non-exclusive rights to manufacture zilebesiran for the development and commercialization of zilebesiran in the Roche Territory. In connection with the Roche Agreement, Roche made an upfront, non-refundable payment of \$310.0 million.

We lead the global clinical development for zilebesiran. We are responsible for forty percent (40%) and Roche is responsible for the remaining sixty percent (60%) of development costs incurred in the conduct of development activities that support regulatory approval of zilebesiran globally. We and Roche share equally (50/50) all costs incurred in connection with development activities that are conducted to support regulatory approval of zilebesiran solely in the Co-Commercialization Territory if incremental development activities are needed. Roche is solely responsible for all costs incurred in the conduct of development activities that are conducted primarily to support regulatory approval in the Roche Territory. Upon regulatory approval, Roche has the exclusive right to commercialize zilebesiran in the Roche Territory and will pay us tiered, low double-digit royalties based on net sales of zilebesiran on a country-by-country basis during the applicable royalty term. We and Roche will co-commercialize zilebesiran in the Co-Commercialization Territory and share equally (50/50) profits and losses (including commercialization costs).

Roche has the right to terminate the Roche Agreement for any or no reason at all upon prior written notice, however, if the termination notice occurs after the achievement of the first development milestone and before the achievement of the third development milestone, Roche is required to pay us a termination fee of \$50.0 million. In addition, either party may terminate the Roche Agreement for a material breach by, or insolvency of, the other party, subject to a cure period. Unless earlier terminated pursuant to its terms, the Roche Agreement commences on the Effective Date and will remain in effect until expiration on a country-by-country basis (a) in the Roche Territory, upon expiration of the applicable royalty term in the applicable country and (b) in the Co-Commercialization Territory, upon expiration of the term of the co-commercialization efforts.

Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any milestone, royalty or profit share payments from Roche under the Roche Agreement.

We evaluated the Roche Agreement and concluded that the Roche Agreement had elements that were within the scope of ASC 606, *Revenue from Contracts with Customers* and ASC 808, *Collaborative Arrangements*.

As of the Effective Date, we identified the following promises in the Roche Agreement that were evaluated under the scope of ASC 606: delivery of (i) a co-exclusive license to develop zilebesiran worldwide and commercialize zilebesiran within the Co-Commercialization Territory, a non-exclusive license to manufacture zilebesiran in the Roche Territory solely for purposes of developing and commercializing zilebesiran in the Roche Territory, and an exclusive license to commercialize zilebesiran in the Roche Territory, collectively referred to as Roche License Obligation, (ii) development services, including the manufacture of clinical supply, that support regulatory approval of zilebesiran, referred to as the Roche Development Services Obligation, and (iii) technology transfer of the existing manufacturing process for zilebesiran, referred to as the Roche Technology Transfer Obligation. The three performance obligations under the Roche Agreement are collectively referred to as the Roche Performance Obligations.

We also evaluated whether certain options outlined within the Roche Agreement represented material rights that would give rise to a performance obligation and concluded that none of the options convey a material right to Roche and therefore were not considered separate performance obligations within the Roche Agreement.

We assessed the above promises and determined that the Roche License Obligation, Roche Development Services Obligation and Roche Technology Transfer Obligation were reflective of a vendor-customer relationship and therefore represented performance obligations within the scope of ASC 606. The Roche License Obligation was considered functional intellectual property and distinct from other promises under the contract as Roche can benefit from the licenses on its own or together with other readily available resources. As the licenses were delivered at the same time, they were considered one performance obligation at contract inception. The Roche Development Services Obligation was considered distinct as Roche could benefit from the development services together with the licenses transferred by us at the inception of the agreement. The development services are not expected to significantly modify or customize the initial intellectual property as zilebesiran was in Phase 2 clinical development at contract inception. The Roche Technology Transfer Obligation was distinct as Roche can benefit from the manufacturing license transferred by us at the inception of the agreement given the advancements of our RNAi platform and our utilization of third-party contract manufacturing organizations to manufacture zilebesiran. Therefore, each represents a separate performance obligation within the contract with a customer under the scope of ASC 606 at contract inception.

We consider the collaborative activities associated with the co-commercialization of zilebesiran in the U.S. to be a separate unit of account within the scope of ASC 808 as we and Roche are both active participants in the commercialization activities

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and are exposed to significant risks and rewards that are dependent on the commercial success of the activities in the arrangement.

We determined the transaction price under ASC 606 at the inception of the Roche Agreement was \$857.0 million, consisting of the \$310.0 million upfront payment and \$547.0 million additional variable consideration attributed to cost reimbursement from development and manufacturing services and technology transfer related to the Roche Performance Obligations. We determined that any variable consideration related to development and regulatory milestones was deemed to be fully constrained at inception and therefore excluded from the initial transaction price due to the high degree of uncertainty and risk associated with these potential payments as we determined that we could not assert that it was probable that a significant reversal in the amount of cumulative revenue recognized would not occur. We also determined that royalties and sales milestones relate solely to the licenses of intellectual property and were therefore excluded from the transaction price under the sales- or usage-based royalty exception of ASC 606.

We developed the estimated standalone selling price at inception for each of the Roche Performance Obligations with the objective of determining the price at which we would sell such an item if it were to be sold regularly on a standalone basis. We developed the estimated standalone selling price for the Roche License Obligation primarily based on the probability-weighted present value of expected future cash flows associated with each underlying license or activity. In developing such estimates, we applied judgment in determining the forecasted revenues, taking into consideration the applicable market conditions and relevant entity-specific factors, the probability of success, the time needed to develop zilebesiran and the discount rate. We developed the estimated standalone selling price for the services and clinical supply included in the Roche Development Services Obligation and the Roche Technology Transfer Obligation primarily based on the level of efforts necessary to perform the service and the costs for full-time equivalent employees and expected resources to be committed plus a reasonable margin.

We allocated the variable consideration related to the estimated reimbursements for the Roche Development Services Obligation and the Roche Technology Transfer Obligation to each performance obligation as the terms of the variable payment relate specifically to our efforts to satisfy the performance obligation and allocating the variable amount of consideration entirely to the respective performance obligation is consistent with the allocation objective of ASC 606 when considering all of the performance obligations and payment terms in the contract. We allocated the fixed up-front consideration of \$310.0 million entirely to the Roche License Obligation as the value of the fixed consideration together with the expected value of the remaining development and regulatory milestones, sales-based milestones, and royalties, all of which are either currently constrained at inception or subject to the sales- or usage-based royalty exception, approximates the standalone selling price of the Roche License Obligation. Therefore, allocating the fixed upfront consideration entirely to the Roche License Obligation is consistent with the allocation objective of ASC 606 when considering all of the performance obligations and payment terms in the contract.

The Roche License Obligation was satisfied at a point in time upon transfer of the license to Roche. Control of the licenses was transferred on the Effective Date and Roche could begin to use and benefit from the licenses. For the Roche Development Services Obligation, we measure proportional performance over time using an input method based on cost incurred relative to the total estimated cost of the obligation, on a quarterly basis, by determining the proportion of effort incurred as a percentage of total effort we expect to expend. This ratio is applied to the transaction price allocated to the obligation. Management has applied significant judgment in the process of developing our estimates. We re-evaluate the transaction price as of the end of each reporting period.

As of March 31, 2024, the total transaction price was determined to be \$922.0 million, an increase of \$65.0 million from December 31, 2023. During the three months ended March 31, 2024, we determined that the most likely amount for the development milestone due to us upon the first patient dosed in the KARDIA-3 Phase 2 study was \$65.0 million and that this development milestone was probable of occurring. Therefore, we recognized \$65.0 million in net revenues from collaborations as the development milestone specifically relates to the transfer of the license to Roche which occurred on the Effective Date. In April 2024, the \$65.0 million development milestone was achieved when the first patient was dosed in the KARDIA-3 Phase 2 study.

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The following tables provide a summary of the transaction price allocated to each performance obligation, in addition to revenue activity during the period, in thousands:

Performance Obligations	Transaction Price Allocated As of March 31, 2024	Revenue Recognized During Three Months Ended March 31,	
		2024	2023
Roche License Obligation	\$ 375,000	\$ 65,000	\$ —
Roche Development Services Obligation	545,000	7,151	—
Roche Technology Transfer Obligation	2,000	—	—
	<u>\$ 922,000</u>	<u>\$ 72,151</u>	<u>\$ —</u>

As of March 31, 2024, the aggregate amount of the transaction price allocated to the Roche Performance Obligations that was unsatisfied was \$515.9 million, which is expected to be recognized through the term of the Roche Agreement as the services are performed.

Regeneron Pharmaceuticals, Inc.

In 2019, we entered into a global, strategic collaboration with Regeneron to discover, develop and commercialize RNAi therapeutics for a broad range of diseases by addressing therapeutic targets expressed in the eye and central nervous system, or CNS, in addition to a select number of targets expressed in the liver, which we refer to as the Regeneron Collaboration. The Regeneron Collaboration is governed by a Master Agreement, referred to as the Regeneron Master Agreement. In connection with the Regeneron Master Agreement, we and Regeneron entered into (i) a co-co collaboration agreement covering the continued development of cemdisiran, our C5 siRNA, currently in development for C5 complement-mediated diseases, as a monotherapy, or the C5 co-co collaboration agreement, and (ii) a license agreement to evaluate anti-C5 antibody-siRNA combinations for C5 complement-mediated diseases including evaluating the combination of Regeneron's pozelimab and cemdisiran, or the C5 license agreement.

Under the terms of the Regeneron Collaboration, we are working exclusively with Regeneron to discover RNAi therapeutics for eye and CNS diseases for an initial research period of approximately five years, which we refer to as the Initial Research Term. Regeneron has an option to extend the Initial Research Term (referred to as the Research Term Extension Period, and together with the Initial Research Term, the Research Term) for up to an additional five years, for a research term extension fee of \$300.0 million. The Regeneron Collaboration also covers a select number of RNAi therapeutic programs designed to target genes expressed in the liver, including our previously announced collaboration with Regeneron to identify RNAi therapeutics for the chronic liver disease nonalcoholic steatohepatitis. We retain broad global rights to all of our other unpartnered liver-directed clinical and pre-clinical pipeline programs. The Regeneron Collaboration is governed by a joint steering committee that is comprised of an equal number of representatives from each party.

Regeneron leads development and commercialization for all programs targeting eye diseases (subject to limited exceptions), entitling us to certain potential milestone and royalty payments pursuant to the terms of a license agreement, the form of which has been agreed upon by the parties. We and Regeneron are alternating leadership on CNS and liver programs covered by the Regeneron Collaboration, with the lead party retaining global development and commercial responsibility. For such CNS and liver programs, both we and Regeneron have the option at lead candidate selection to enter into a co-co collaboration agreement, the form of which has been agreed upon by the parties, whereby both companies will share equally all costs of, and profits from, all development and commercialization activities under the program. If the non-lead party elects to not enter into a co-co collaboration agreement with respect to a given CNS or liver program, we and Regeneron will enter into a license agreement with respect to such program and the lead party will be the "Licensee" for the purposes of the license agreement. If the lead party for a CNS or liver program elects to not enter into the co-co collaboration agreement, then we and Regeneron will enter into a license agreement with respect to such program and leadership of the program will transfer to the other party and the former non-lead party will be the "Licensee" for the purposes of the license agreement.

With respect to the programs directed to C5 complement-mediated diseases, we retain control of cemdisiran monotherapy development, and Regeneron is leading combination product development. Pursuant to the C5 co-co collaboration agreement, Regeneron notified us in November 2022 of its decision to exercise its right to opt-out of the further development and commercialization of cemdisiran monotherapy. As a result, Regeneron no longer shares costs and potential future profits on any monotherapy program with us. We continue to perform our obligations under the agreement, and we are solely responsible for all development and commercialization costs. Regeneron will be eligible to receive tiered double-digit royalties on net sales. Under the C5 license agreement, for cemdisiran to be used as part of a combination product, Regeneron is solely responsible for all development and commercialization costs, and we will receive low double-digit royalties and commercial milestones of up to \$325.0 million on any potential combination product sales. The C5 co-co collaboration agreement, the C5 license agreement, and the Regeneron Master Agreement have been combined for accounting purposes and treated as a single agreement.

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In connection with the Regeneron Master Agreement, Regeneron made an upfront payment of \$400.0 million. In 2023, we received a \$100.0 million milestone payment upon satisfying criteria during early clinical development for our CNS program, mivelsiran (formerly ALN-APP). We are also eligible to receive up to an additional \$100.0 million in milestone payments upon achievement of certain criteria during early clinical development for an eye program. We and Regeneron plan to advance programs directed to up to 30 targets in the first five years under the Regeneron Collaboration during the Initial Research Term. For each program, Regeneron will provide us with \$2.5 million in funding at program initiation and an additional \$2.5 million at lead candidate identification, with the potential for approximately \$30.0 million in annual discovery funding to us as the Regeneron Collaboration reaches steady state.

Regeneron has the right to terminate the Regeneron Master Agreement for convenience upon ninety days' notice. The termination of the Regeneron Master Agreement does not affect the term of any license agreement or co-co collaboration agreement then in effect. In addition, either party may terminate the Regeneron Master Agreement for a material breach by, or insolvency of, the other party. Unless earlier terminated pursuant to its terms, the Regeneron Master Agreement will remain in effect with respect to each program until (a) such program becomes a terminated program or (b) the parties enter into a license agreement or co-co collaboration agreement with respect to such program. The Regeneron Master Agreement includes various representations, warranties, covenants, dispute escalation and resolution mechanisms, indemnities and other provisions customary for transactions of this nature.

For any license agreement subsequently entered into, the licensee will generally be responsible for its own costs and expenses incurred in connection with the development and commercialization of the collaboration products. The licensee will pay to the licensor certain development and/or commercialization milestone payments totaling up to \$150.0 million for each collaboration product. In addition, following the first commercial sale of the applicable collaboration product under a license agreement, the licensee is required to make certain tiered royalty payments, ranging from low double-digits up to 20%, to the licensor based on the aggregate annual net sales of the collaboration product, subject to customary reductions.

For any co-co collaboration agreement subsequently entered into, we and Regeneron will share equally all costs of, and profits from, development and commercialization activities. Reimbursement of our share of costs will be recognized as a reduction to research and development expense in the condensed consolidated statements of operations and comprehensive loss. In the event that a party exercises its opt-out right, the lead party will be responsible for all costs and expenses incurred in connection with the development and commercialization of the collaboration products under the applicable co-co collaboration agreement, subject to continued sharing of costs through defined points. If a party exercises its opt-out right, following the first commercial sale of the applicable collaboration product under a co-co collaboration agreement, the lead party is required to make certain tiered royalty payments, ranging from low double-digits up to 20%, to the other party based on the aggregate annual net sales of the collaboration product and the timing of the exercise of the opt-out right, subject to customary reductions and a reduction for opt-out transition costs.

Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any additional milestone or royalty payments from Regeneron under the Regeneron Master Agreement, the C5 license agreement, or any future license agreement, or under any co-co collaboration agreement in the event we exercise our opt-out right.

Our obligations under the Regeneron Collaboration include: (i) a research license and research services, collectively referred to as the Research Services Obligation; (ii) a worldwide license to cemdisiran for combination therapies, and manufacturing and supply, and development service obligations, collectively referred to as the C5 License Obligation; and (iii) development, manufacturing and commercialization activities for cemdisiran monotherapies, referred to as the C5 Co-Co Obligation.

We determined the research license was not distinct from the research services primarily as a result of Regeneron being unable to benefit on its own or with other resources reasonably available, as the license is providing access to specialized expertise, particularly as it relates to RNAi technology, which was not available in the marketplace when the Regeneron Collaboration was executed. Similarly, the worldwide license to cemdisiran for combination therapies was not distinct from the manufacturing and supply, and development service obligations, as Regeneron cannot benefit on its own from the value of the license without receipt of supply.

Separately, prior to Regeneron's decision in November 2022 to exercise its right to opt-out of the further development and commercialization of cemdisiran monotherapy, the C5 co-co collaboration agreement was under the scope of ASC 808 as we and Regeneron were both active participants in the development and manufacturing activities and were exposed to significant risks and rewards that were dependent on commercial success of the activities of the arrangement. Regeneron's decision to exercise its right to opt-out of the arrangement caused a change in the role of Regeneron and its exposure to significant risks and rewards under the arrangement. As a result, we determined that the arrangement no longer represents a collaborative arrangement.

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The arrangement now represents a vendor-customer relationship under ASC 606 as we perform our obligation to provide development and manufacturing activities under the arrangement. The transaction price allocated to the C5 Co-Co obligation unit of account is recognized over time using an input method based on cost incurred relative to the total estimated costs for the identified performance obligation by determining the proportion of effort incurred as a percentage of total effort we expect to expend.

The total transaction price is comprised of the \$400.0 million upfront payment and additional variable consideration related to research, development, manufacturing and supply activities related to the Research Services Obligation and the C5 License Obligation. We utilized the expected value method to determine the amount of reimbursement for these activities. We determined that any variable consideration related to sales-based royalties and milestones related to the worldwide license to cemdisiran for combination therapies is deemed to be constrained and therefore has been excluded from the transaction price. In addition, we are eligible to receive a future milestone payment upon the achievement of certain criteria during early clinical development for an eye program. We are also eligible to receive royalties on future commercial sales for certain eye, CNS or liver targets, if any; however, these amounts are excluded from variable consideration under the Regeneron Collaboration as we are only eligible to receive such amounts if, after a drug candidate is identified, the form of license agreement is subsequently executed resulting in a license that is granted to Regeneron. Any such subsequently granted license would represent a separate transaction under ASC 606.

We allocated the initial transaction price to each unit of account based on the applicable accounting guidance as follows, in thousands:

<u>Performance Obligations</u>	<u>Standalone Selling Price</u>	<u>Transaction Price Allocated</u>
Research Services Obligation	\$ 130,700	\$ 183,100
C5 License Obligation	\$ 97,600	92,500
C5 Co-Co Obligation	\$ 364,600	246,000
		<u>\$ 521,600</u>

The transaction price was allocated to the obligations based on the relative estimated standalone selling prices of each obligation, over which management has applied significant judgment. We developed the estimated standalone selling price for the licenses included in the Research Services Obligation and the C5 License Obligation primarily based on the probability-weighted present value of expected future cash flows associated with each license related to each specific program. In developing such estimate, we applied judgment in the determination of the forecasted revenues, taking into consideration the applicable market conditions and relevant entity-specific factors, the expected number of targets or indications expected to be pursued under each license, the probability of success, the time needed to develop a product candidate pursuant to the associated license and the discount rate. We developed the estimated standalone selling price for the services and/or manufacturing and supply included in each of the obligations, as applicable, primarily based on the nature of the services to be performed and/or goods to be manufactured and estimates of the associated costs. The estimated standalone selling price of the C5 Co-Co Obligation was developed by estimating the present value of expected future cash flows that Regeneron is entitled to receive. In developing such estimate, we applied judgment in determining the indications that will be pursued, the forecasted revenues for such indications, the probability of success and the discount rate.

For the Research Services Obligation, the C5 License Obligation, and the C5 Co-Co Obligation accounted for under ASC 606, we measure proportional performance over time using an input method based on cost incurred relative to the total estimated costs for each of the identified obligations, on a quarterly basis, by determining the proportion of effort incurred as a percentage of total effort we expect to expend. This ratio is applied to the transaction price allocated to each obligation. Management has applied significant judgment in the process of developing our estimates. Any changes to these estimates will be recognized in the period in which they change as a cumulative catch up. We re-evaluate the transaction price as of the end of each reporting period and as of March 31, 2024, the total transaction price was determined to be \$676.3 million, an immaterial increase from December 31, 2023. As of March 31, 2024, the transaction price is comprised of the upfront payment and variable consideration related to development, manufacture, and supply activities. Revenue recognized under this agreement is accounted for as collaboration revenue.

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The following tables provide a summary of the transaction price allocated to each unit of account based on the applicable accounting guidance, in addition to revenue activity during the period and deferred revenue as of the balance sheet date, in thousands:

Performance Obligations	Transaction Price Allocated		Deferred Revenue		
	As of March 31, 2024		As of March 31, 2024		As of December 31, 2023
Research Services Obligation	\$	305,680	\$	48,700	\$ 63,400
C5 License Obligation		124,600		26,100	27,500
C5 Co-Co Obligation		246,000		185,500	186,200
	\$	676,280	\$	260,300	\$ 277,100

Performance Obligations	Revenue Recognized During			
	Three Months Ended March 31,			
	2024		2023	
Research Services Obligation	\$	14,700	\$	10,700
C5 License Obligation		1,700		2,200
C5 Co-Co Obligation		700		2,500
	\$	17,100	\$	15,400

As of March 31, 2024, the aggregate amount of the transaction price allocated to the remaining Research Services Obligation, C5 License Obligation, and C5 Co-Co Obligation that was unsatisfied was \$318.1 million, which is expected to be recognized through the term of the Regeneron Collaboration as the services are performed. Deferred revenue related to the Regeneron Collaboration is classified as either current or non-current in the condensed consolidated balance sheets based on the period the revenue is expected to be recognized.

Novartis AG

2013 Collaboration with The Medicines Company

In February 2013, we and The Medicines Company, or MDCO, entered into a license and collaboration agreement pursuant to which we granted to MDCO an exclusive, worldwide license to develop, manufacture and commercialize RNAi therapeutics targeting proprotein convertase subtilisin/kexin type 9 for the treatment of hypercholesterolemia and other human diseases, including inclisiran. We refer to this agreement, as amended through the date hereof, as the MDCO License Agreement. In 2020, Novartis AG, or Novartis, completed its acquisition of MDCO and assumed all of MDCO's rights and obligations under the MDCO License Agreement.

As of March 31, 2024, we have earned \$120.0 million of milestones and we could be entitled to receive an additional \$60.0 million commercialization milestone. In addition, we are entitled to royalties ranging from 10% up to 20% based on annual worldwide net sales of licensed products by Novartis, its affiliates and sublicensees, subject to reduction under specified circumstances. Due to the uncertainty of future commercial sales of Leqvio by Novartis, we may not receive any additional milestone payments under the MDCO License Agreement and future royalty payments may be less than anticipated.

Other

In addition to the collaboration agreements discussed above, we have various other collaboration agreements that are not individually significant to our operating results or financial condition at this time. Pursuant to the terms of those agreements, we may be required to pay, or we may receive, additional amounts contingent upon the occurrence of various future events (e.g., upon the achievement of various development and commercial milestones) which in the aggregate could be significant. We may also incur, or be reimbursed for, significant research and development costs. In addition, if any products related to these collaborations are approved for sale, we may be required to pay, or we may receive, royalties on future sales. The payment or receipt of these amounts, however, is contingent upon the occurrence of various future events.

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5. FAIR VALUE MEASUREMENTS

The following tables present information about our financial assets and liabilities that are measured at fair value on a recurring basis and indicate the fair value hierarchy of the valuation techniques we utilized to determine such fair value:

(In thousands)	As of March 31, 2024	Quoted Prices in Active Markets (Level 1)	Significant Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Financial assets				
Cash equivalents:				
Money market funds	\$ 126,550	\$ 126,550	\$ —	\$ —
U.S. treasury securities	47,797	—	47,797	—
Commercial paper	8,971	—	8,971	—
Marketable debt securities:				
U.S. treasury securities	913,875	—	913,875	—
U.S. government-sponsored enterprise securities	427,513	—	427,513	—
Corporate notes	263,468	—	263,468	—
Commercial paper	73,291	—	73,291	—
Marketable equity securities	11,256	11,256	—	—
Restricted cash (money market funds)	1,214	1,214	—	—
Total financial assets	\$ 1,873,935	\$ 139,020	\$ 1,734,915	\$ —
Financial liabilities				
Development derivative liability	\$ 336,579	\$ —	\$ —	\$ 336,579

(In thousands)	As of December 31, 2023	Quoted Prices in Active Markets (Level 1)	Significant Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Financial assets				
Cash equivalents:				
Money market funds	\$ 166,059	\$ 166,059	\$ —	\$ —
U.S. treasury securities	30,712	—	30,712	—
Commercial paper	2,685	—	2,685	—
Corporate notes	762	—	762	—
Marketable debt securities:				
U.S. treasury securities	862,022	—	862,022	—
U.S. government-sponsored enterprise securities	441,341	—	441,341	—
Corporate notes	252,350	—	252,350	—
Commercial paper	56,216	—	56,216	—
Certificates of deposit	3,587	—	3,587	—
Marketable equity securities	11,178	11,178	—	—
Restricted cash (money market funds)	1,210	1,210	—	—
Total financial assets	\$ 1,828,122	\$ 178,447	\$ 1,649,675	\$ —
Financial liabilities				
Development derivative liability	\$ 324,941	\$ —	\$ —	\$ 324,941

For the three months ended March 31, 2024 and 2023, there were no transfers into or out of Level 3 financial assets or liabilities. The carrying amounts reflected on our condensed consolidated balance sheets for cash, accounts receivable, net, other current assets, accounts payable and accrued expenses approximate fair value due to their short-term maturities.

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6. MARKETABLE DEBT SECURITIES

We invest our excess cash balances in marketable debt securities and at each balance sheet date presented, we classify all of our investments in debt securities as available-for-sale and as current assets as they represent the investment of funds available for current operations. We did not record any impairment charges related to our marketable debt securities during the three months ended March 31, 2024 or 2023.

The following tables summarize our marketable debt securities:

(In thousands)	As of March 31, 2024			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
U.S. treasury securities	\$ 963,082	\$ 74	\$ (1,484)	\$ 961,672
U.S. government-sponsored enterprise securities	427,918	200	(605)	427,513
Corporate notes	263,673	208	(413)	263,468
Commercial paper	82,262	—	—	82,262
Total	<u>\$ 1,736,935</u>	<u>\$ 482</u>	<u>\$ (2,502)</u>	<u>\$ 1,734,915</u>

(In thousands)	As of December 31, 2023			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
U.S. treasury securities	\$ 892,237	\$ 1,085	\$ (588)	\$ 892,734
U.S. government-sponsored enterprise securities	440,915	1,000	(574)	441,341
Corporate notes	252,487	945	(320)	253,112
Commercial paper	58,901	—	—	58,901
Certificates of deposit	3,587	—	—	3,587
Total	<u>\$ 1,648,127</u>	<u>\$ 3,030</u>	<u>\$ (1,482)</u>	<u>\$ 1,649,675</u>

The fair values of our marketable debt securities by classification in the condensed consolidated balance sheets were as follows:

(In thousands)	As of March 31, 2024		As of December 31, 2023	
	Amortized Cost	Fair Value	Amortized Cost	Fair Value
Marketable debt securities	\$ 1,678,147	\$ 1,615,516	\$ 1,648,127	\$ 1,649,675
Cash and cash equivalents	56,768	34,159	—	—
Total	<u>\$ 1,734,915</u>	<u>\$ 1,649,675</u>	<u>\$ 1,648,127</u>	<u>\$ 1,649,675</u>

7. OTHER BALANCE SHEET DETAILS

Inventory

The components of inventory are summarized as follows:

(In thousands)	As of March 31, 2024		As of December 31, 2023	
	Amortized Cost	Fair Value	Amortized Cost	Fair Value
Raw materials	\$ 25,401	\$ 23,346	\$ 25,401	\$ 23,346
Work in process	76,071	76,963	76,071	76,963
Finished goods	24,819	25,123	24,819	25,123
Total inventory	<u>\$ 126,291</u>	<u>\$ 125,432</u>	<u>\$ 126,291</u>	<u>\$ 125,432</u>

As of March 31, 2024 and December 31, 2023, we had \$32.3 million and \$36.3 million of long-term inventory, respectively, included within other assets in our condensed consolidated balance sheets as we anticipate it being consumed beyond our normal operating cycle.

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Cash, Cash Equivalents and Restricted Cash

The following table provides a reconciliation of cash, cash equivalents and restricted cash reported within our condensed consolidated balance sheets that sum to the total of these amounts shown in the condensed consolidated statements of cash flows:

(In thousands)	As of March 31,	
	2024	2023
Cash and cash equivalents	\$ 681,879	\$ 672,245
Total restricted cash included in other assets	2,840	2,166
Total cash, cash equivalents, and restricted cash shown in the condensed consolidated statements of cash flows	<u>\$ 684,719</u>	<u>\$ 674,411</u>

Accumulated Other Comprehensive (Loss) Income

The following tables summarize the changes in accumulated other comprehensive (loss) income, by component:

(In thousands)	Loss on Investment in Joint Venture	Defined Benefit Pension Plans	Unrealized (Losses) Gains from Debt Securities	Foreign Currency Translation Adjustment	Total Accumulated Other Comprehensive Loss
Balance as of December 31, 2023	\$ (32,792)	\$ (2,753)	\$ 1,548	\$ 10,622	\$ (23,375)
Other comprehensive loss before reclassifications	—	—	(6)	(78)	(84)
Amounts reclassified from other comprehensive loss	—	33	(3,562)	—	(3,529)
Net other comprehensive loss	—	33	(3,568)	(78)	(3,613)
Balance as of March 31, 2024	<u>\$ (32,792)</u>	<u>\$ (2,720)</u>	<u>\$ (2,020)</u>	<u>\$ 10,544</u>	<u>\$ (26,988)</u>

(In thousands)	Loss on Investment in Joint Venture	Defined Benefit Pension Plans	Unrealized (Losses) Gains from Debt Securities	Foreign Currency Translation Adjustment	Total Accumulated Other Comprehensive Loss
Balance as of December 31, 2022	\$ (32,792)	\$ (1,092)	\$ (9,470)	\$ (1,300)	\$ (44,654)
Other comprehensive income before reclassifications	—	—	(9)	1,410	1,401
Amounts reclassified from other comprehensive income	—	(5)	4,134	—	4,129
Net other comprehensive income	—	(5)	4,125	1,410	5,530
Balance as of March 31, 2023	<u>\$ (32,792)</u>	<u>\$ (1,097)</u>	<u>\$ (5,345)</u>	<u>\$ 110</u>	<u>\$ (39,124)</u>

Amounts reclassified out of accumulated other comprehensive (loss) income relate to settlements of marketable debt securities and amortization of our pension obligation which are recorded within other expense, net in the condensed consolidated statements of operations and comprehensive loss.

8. CONVERTIBLE DEBT

Convertible Senior Notes Due 2027

In 2022, we commenced a private offering of \$900.0 million in aggregate principal amount of 1% Convertible Senior Notes due 2027, or the Initial Notes. On September 13, 2022, the initial purchasers in such offering exercised their option to purchase an additional \$135.0 million in aggregate principal amount of our 1% Convertible Senior Notes due 2027, or the Additional Notes, and together with the Initial Notes collectively referred to as the Notes, bringing the total aggregate principal amount of the Notes to \$1.04 billion. The Notes were issued pursuant to an indenture, dated September 15, 2022, or the Indenture. The Indenture includes customary covenants and sets forth certain events of default after which the Notes may be declared immediately due and payable and sets forth certain types of bankruptcy or insolvency events of default involving the Company after which the Notes become automatically due and payable.

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The Notes will mature on September 15, 2027, unless earlier converted, redeemed or repurchased. The Notes will bear interest from September 15, 2022 at a rate of 1% per year payable semiannually in arrears on March 15 and September 15 of each year, beginning on March 15, 2023. The Notes are convertible at the option of the noteholder on or after June 15, 2027. Prior to June 15, 2027, the Notes are convertible only under the following circumstances: (1) During any calendar quarter commencing after the calendar quarter ending on December 31, 2022 (and only during such calendar quarter), if the last reported sale price of our common stock for at least 20 trading days (whether or not consecutive) during a period of 30 consecutive trading days ending on, and including, the last trading day of the immediately preceding calendar quarter is greater than or equal to 130% of the conversion price on each applicable trading day; (2) During the five business day period after any ten consecutive trading day period in which the trading price per \$1,000 principal amount of the Notes for each trading day of that ten consecutive trading day period was less than 98% of the product of the last reported sale price of our common stock and the conversion rate of the Notes on such trading day; (3) If we call any or all of the Notes for redemption; or (4) Upon the occurrence of specific corporate events as set forth in the Indenture governing the Notes. We will settle any conversions of Notes by paying or delivering, as applicable, cash, shares of our common stock, or a combination of cash and shares of common stock, at our election.

The conversion rate for the Notes will initially be 3.4941 shares of common stock per \$1,000 principal amount of Notes, which is equivalent to an initial conversion price of approximately \$286.20 per share of common stock. The initial conversion price of the Notes represents a premium of approximately 35% over the \$212.00 per share last reported sale price of common stock on September 12, 2022. The conversion rate is subject to adjustment under certain circumstances in accordance with the terms of the Indenture.

We may not redeem the Notes prior to September 20, 2025. We may redeem for cash equal to 100% of the principal amount of the Notes being redeemed plus accrued and unpaid interest of all or any portion of the Notes, at our option, on or after September 20, 2025, if the last reported sales price of our common stock has been at least 130% of the conversion price then in effect for at least 20 trading days (whether or not consecutive) during any 30 consecutive trading day period. No sinking fund is provided for the Notes and therefore we are not required to redeem or retire the Notes periodically.

If we undergo a fundamental change, as defined in the indenture agreement, then subject to certain conditions, holders may require us to repurchase for cash all or any portion of their Notes at a fundamental change repurchase price equal to 100% of the principal amount of the Notes to be repurchased plus accrued and unpaid interest. In addition, if specific corporate events occur prior to the maturity date or if we issue a notice of redemption, we will increase the conversion rate by pre-defined amounts for holders who elect to convert their notes in connection with such corporate event. The conditions allowing holders of the Notes to convert were not met this quarter.

As of March 31, 2024, the Notes are classified as a long-term liability, net of issuance costs of \$19.2 million, on the condensed consolidated balance sheets. As of March 31, 2024, the estimated fair value of the Notes was approximately \$979.4 million. The fair value was determined based on the last actively traded price per \$100 of the Notes for the three months ended March 31, 2024 (Level 2). The Notes were issued at par and costs associated with the issuance of the Notes are amortized to interest expense over the contractual term of the Notes. As of March 31, 2024, the effective interest rate of the Notes is 1%.

Capped Call Transactions

In 2022, in connection with the pricing of the Initial Notes and the initial purchasers' exercise of their option to purchase the Additional Notes, we entered into privately negotiated capped call transactions, or Capped Call Transactions. The Capped Call Transactions initially cover, subject to customary anti-dilution adjustments, the number of shares of common stock that underlie the Notes. The cap price of the Capped Call Transactions is initially \$424.00 per share, which represents a premium of 100% over the last reported sale price of common stock of \$212.00 per share on September 12, 2022, and is subject to certain adjustments under the terms of the Capped Call Transactions.

9. LIABILITY RELATED TO THE SALE OF FUTURE ROYALTIES

In April 2020, we entered into a purchase and sale agreement, or Purchase Agreement, with BX Bodyguard Royalties L.P. (an affiliate of The Blackstone Group Inc.), or Blackstone Royalties, under which Blackstone Royalties acquired a percentage of royalties payable, or the Royalty Interest, initially set at 50% with respect to net sales by MDCO, its affiliates or sublicensees of inclisiran (or the branded drug product, Leqvio) and any other licensed products under the MDCO License Agreement, and 75% of the commercial milestone payments payable under the MDCO License Agreement, together with the Royalty Interest, the Purchased Interest. If Blackstone Royalties does not receive payments in respect of the Royalty Interest by December 31, 2029, equaling at least \$1.00 billion, Blackstone Royalties will receive the Royalty Interest at 55% beginning on January 1, 2030. In consideration for the sale of the Purchased Interest, Blackstone Royalties paid us \$1.00 billion.

We continue to own or control all inclisiran intellectual property rights and are responsible for certain ongoing manufacturing and supply obligations related to the generation of the Purchased Interest. Due to our continuing involvement,

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we will continue to account for any royalties and commercial milestones due to us under the MDCO License Agreement as revenue on our condensed consolidated statement of operations and comprehensive loss and record the proceeds from this transaction as a liability, net of closing costs, on our condensed consolidated balance sheet.

In order to determine the amortization of the liability related to the sale of future royalties, we are required to estimate the total amount of future payments to Blackstone Royalties over the life of the Purchase Agreement. The \$1.00 billion liability, recorded at execution of the agreement, will be accreted to the total of these royalty and commercial milestone payments as interest expense over the life of the Purchase Agreement. As of March 31, 2024, our estimate of this total interest expense resulted in an effective annual interest rate of 9%. These estimates contain assumptions that impact both the amount recorded at execution and the interest expense that will be recognized in future periods.

As payments are made to Blackstone Royalties, the balance of the liability will be effectively repaid over the life of the Purchase Agreement. The exact timing and amount of repayment is likely to change each reporting period. A significant increase or decrease in Leqvio global net revenue will materially impact the liability related to the sale of future royalties, interest expense and the time period for repayment. We will periodically assess the expected payments to Blackstone Royalties and to the extent the amount or timing of such payments is materially different than our initial estimates, we will prospectively adjust the amortization of the liability related to the sale of future royalties and the related interest expense.

As of March 31, 2024, the carrying value of the liability related to the sale of future royalties was \$1.38 billion, net of closing costs of \$9.8 million. The carrying value of the liability related to the sale of future royalties approximates fair value as of March 31, 2024 and is based on our current estimates of future royalties and commercial milestones expected to be paid to Blackstone Royalties over the life of the arrangement, which are considered Level 3 inputs.

The following table shows the activity with respect to the liability related to the sale of future royalties, in thousands:

Carrying value as of December 31, 2023	\$ 1,377,239
Interest expense recognized	31,565
Payments	<u>(25,738)</u>
Carrying value as of March 31, 2024	<u>\$ 1,383,066</u>

10. DEVELOPMENT DERIVATIVE LIABILITY

In August 2020, we entered into a co-development agreement, referred to as the Funding Agreement, with BXLS V Bodyguard – PCP L.P. and BXLS Family Investment Partnership V – ESC L.P., collectively referred to as Blackstone Life Sciences, pursuant to which Blackstone Life Sciences will provide up to \$150.0 million in funding for the clinical development of vutrisiran and zilebesiran, two of our cardiometabolic programs. With respect to vutrisiran, Blackstone Life Sciences has committed to provide up to \$70.0 million to fund development costs related to the HELIOS-B Phase 3 clinical trial. In November 2021, Blackstone Life Sciences opted in to Phase 2 clinical trial funding of zilebesiran, committing to fund, upon meeting certain patient enrollment thresholds, up to \$26.0 million. Furthermore, Blackstone Life Sciences has the right, but is not obligated, to fund up to \$54.0 million for development costs related to a Phase 3 clinical trial of zilebesiran. The amount of funding ultimately provided by Blackstone Life Sciences is dependent on us achieving specified development milestones with respect to each clinical trial. As between Blackstone and the Company, we retain sole responsibility for the development and commercialization of both vutrisiran and zilebesiran.

As consideration for Blackstone Life Sciences' funding for vutrisiran clinical development costs, we have agreed to pay Blackstone Life Sciences a 1% royalty on net sales of AMVUTTRA (vutrisiran) for a 10-year term beginning upon the first commercial sale following regulatory approval of vutrisiran for ATTR-cardiomyopathy, as well as fixed payments of up to 2.5 times their investment over a two-year period upon regulatory approval of vutrisiran for ATTR-cardiomyopathy in specified countries, unless vutrisiran is later withdrawn from the market following a mandatory recall. As consideration for Blackstone Life Sciences' funding for Phase 2 clinical development costs of zilebesiran, we have agreed to pay Blackstone Life Sciences fixed payments of up to 3.25 times their Phase 2 investment over a four-year period upon the successful completion of the zilebesiran Phase 2 clinical trial, unless certain regulatory events affecting the continued development of zilebesiran occur. In September 2023, we announced positive topline results from the KARDIA-1 Phase 2 study of zilebesiran, triggering the achievement of a development milestone of \$84.5 million payable to Blackstone in 16 equal, quarterly payments over four years. As consideration for Blackstone Life Sciences' funding for Phase 3 clinical development costs of zilebesiran, we have agreed to pay Blackstone Life Sciences fixed payments of up to 4.5 times their Phase 3 investment over a four-year period upon regulatory approval of zilebesiran in specified countries, unless it is later withdrawn from the market following a mandatory recall.

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Our payment obligations under the Funding Agreement will be secured, subject to certain exceptions, by security interests in intellectual property owned by us relating to vutrisiran and zilebesiran, as well as in our bank account in which the funding deposits will be made.

We and Blackstone Life Sciences each have the right to terminate the Funding Agreement in its entirety in the event of the other party's bankruptcy or similar proceedings. We and Blackstone Life Sciences may each terminate the Funding Agreement in its entirety or with respect to either product in the event of an uncured material breach by the other party, or with respect to a product for certain patient health and safety reasons, or if regulatory approval in specified major market countries is not obtained for the product following the completion of clinical trials for the product. In addition, Blackstone Life Sciences has the right to terminate the Funding Agreement in its entirety upon the occurrence of certain events affecting our ability to make payments under the agreement or to develop or commercialize the products, or upon a change of control of us. Blackstone Life Sciences may also terminate the Funding Agreement with respect to a product if the joint steering committee elects to terminate the development program for that product in its entirety, if certain clinical endpoints are not achieved for that product or, with respect to vutrisiran only, if our right to develop or commercialize vutrisiran is enjoined in a specified major market as a result of an alleged patent infringement. In certain termination circumstances, we will be obligated to pay Blackstone Life Sciences an amount that is equal to, or a multiplier of, the development funding received from Blackstone Life Sciences, and we may remain obligated under certain circumstances to make the payments to Blackstone Life Sciences described above, or the royalty described above in the case of AMVUTTRA, should we obtain regulatory approval for zilebesiran or vutrisiran for ATTR amyloidosis with cardiomyopathy following termination.

We account for the Funding Agreement under ASC 815, Derivatives and Hedging, as a derivative liability, measured at fair value, recorded within accrued expenses or other liabilities on our condensed consolidated balance sheets, depending on timing of our payment to Blackstone Life Sciences. The change in fair value due to the remeasurement of the development derivative liability is recorded as other expense on our condensed consolidated statements of operations and comprehensive loss.

As of March 31, 2024, the derivative liability is classified as a Level 3 financial liability in the fair value hierarchy. The valuation method incorporates certain unobservable Level 3 key inputs including (i) the probability and timing of achieving stated development milestones to receive payments from Blackstone Life Sciences, (ii) the probability and timing of achieving regulatory approval and payments to Blackstone Life Sciences, (iii) an estimate of the amount and timing of the royalty payable on net sales of AMVUTTRA, assuming regulatory approval for ATTR amyloidosis with cardiomyopathy, (iv) our cost of borrowing (11%), and (v) Blackstone Life Sciences' cost of borrowing (6%).

The following table presents the activity with respect to the development derivative liability, in thousands:

Carrying value as of December 31, 2023	\$	324,941
Amount received under the Funding Agreement		8,333
Amount paid under the Funding Agreement		(5,281)
Change in fair value of development derivative liability		8,586
Carrying value as of March 31, 2024	\$	<u>336,579</u>

11. STOCK-BASED COMPENSATION

The following table summarizes stock-based compensation expenses included in operating costs and expenses on our condensed consolidated statements of operations, and stock-based compensation charges included in additional paid-in capital on our condensed consolidated statements of stockholders' deficit:

(In thousands)	Three Months Ended March 31,	
	2024	2023
Research and development	\$ 19,215	\$ 16,232
Selling, general and administrative	26,132	23,715
Total stock-based compensation expense	<u>45,347</u>	<u>39,947</u>
Capitalized stock-based compensation costs	808	1,189
Total stock-based compensation charges	<u>\$ 46,155</u>	<u>\$ 41,136</u>

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12. NET LOSS PER COMMON SHARE

We compute basic net loss per common share by dividing net loss by the weighted-average number of common shares outstanding. We compute diluted net loss per common share by dividing net loss by the weighted-average number of common shares and dilutive potential common share equivalents then outstanding during the period. In the diluted net loss per share calculation, net loss is adjusted for the elimination of interest expense on the convertible debt. Potential common shares consist of shares issuable upon the vesting of restricted stock units, the exercise of stock options (the proceeds of which are then assumed to have been used to repurchase outstanding shares using the treasury stock method) and upon conversion of the convertible debt outstanding during the period (calculated using the if-converted method assuming the conversion of the convertible debt as of the earliest period reported or at the date of issuance, if later). Because the inclusion of potential common shares would be anti-dilutive for periods presenting a net loss, diluted net loss per common share is the same as basic net loss per common share.

The following table sets forth the potential common shares (prior to consideration of the treasury stock or if-converted methods) excluded from the calculation of net loss per common share because their inclusion would be anti-dilutive:

(In thousands)	Three Months Ended March 31,	
	2024	2023
Options to purchase common stock, inclusive of performance-based stock options	7,538	8,428
Unvested restricted stock units, inclusive of performance-based restricted stock units	3,150	2,547
Convertible debt	3,616	3,616
Total	14,304	14,591

13. COMMITMENTS AND CONTINGENCIES

Technology License and Other Commitments

We have licensed from third parties the rights to use certain technologies and information in our research processes as well as in any other products we may develop. In accordance with the related license or technology agreements, we are required to make certain fixed payments to the licensor or a designee of the licensor over various agreement terms. Many of these agreement terms are consistent with the remaining lives of the underlying intellectual property that we have licensed. As of March 31, 2024, our commitments over the next five years to make fixed and cancellable payments under existing license agreements were not material.

Legal Matters

From time to time, we may be a party to litigation, arbitration or other legal proceedings in the course of our business, including the matters described below. The claims and legal proceedings in which we could be involved include challenges to the scope, validity or enforceability of patents relating to our products or product candidates, and challenges by us to the scope, validity or enforceability of the patents held by others. These include claims by third parties that we infringe their patents or breach our license or other agreements with such third parties. The outcome of any such legal proceedings, regardless of the merits, is inherently uncertain. In addition, litigation and related matters are costly and may divert the attention of our management and other resources that would otherwise be engaged in other activities. If we were unable to prevail in any such legal proceedings, our business, results of operations, liquidity and financial condition could be adversely affected. Our accounting policy for accrual of legal costs is to recognize such expenses as incurred.

Patent Infringement Lawsuits

In March 2022, we filed separate lawsuits in the U.S. District Court for the District of Delaware against (1) Pfizer, Inc. and its subsidiary Pharmacia & Upjohn Co. LLC, collectively referred to as Pfizer, and (2) Moderna, Inc. and its subsidiaries ModernaTX, Inc., and Moderna US, Inc., collectively referred to as Moderna. The lawsuits seek damages for infringement of U.S. Patent No. 11,246,933, or '933 Patent, in Pfizer's and Moderna's manufacture and sale of their messenger RNA, or mRNA, COVID-19 vaccines. The patent relates to the Company's biodegradable cationic lipids that are foundational to the success of the mRNA COVID-19 vaccines.

We are seeking judgment that each of Pfizer and Moderna is infringing the '933 Patent, as well as damages adequate to compensate for the infringement, but in no event less than a reasonable royalty for the unlicensed uses made of our patented lipids by Pfizer and Moderna, together with interest and costs as may be awarded by the court. As stated in the filed complaints, we are not seeking injunctive relief in these lawsuits.

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On May 23, 2022, Moderna filed a partial motion to dismiss, asserting an affirmative defense under Section 1498(a). We responded on May 27, 2022, opposing their motion arguing Moderna had significant non-government sales and the government contract ended in April 2022. Moderna responded on June 13, 2022, requesting a partial motion to dismiss those claims for sales under Section 1498(a).

On May 27, 2022, Pfizer filed an answer to our complaint, denying the allegations, and asserting invalidity and non-infringement defenses. In addition, Pfizer added BioNTech SE to the suit and added counter-claims seeking a declaratory judgment that our patent is invalid and a second claim alleging that our patent is invalid due to patent misuse. We believe their defenses and counter-claims have no merit and responded on June 10, 2022, with substantive arguments as to the validity of our claims and the lack of merit of their patent misuse claim.

On July 12, 2022, we filed an additional lawsuit against each of Pfizer and Moderna seeking damages for infringement of U.S. Patent No. 11,382,979, or '979 patent, in Pfizer's and Moderna's manufacture and sale of their mRNA COVID-19 vaccines. The parties agreed to combine the two patents in one lawsuit, separately against each of Moderna and Pfizer/BioNTech.

On February 8, 2023, we received notification from the U.S. Patent Office that a third patent would issue on February 28, 2023, as U.S. Patent No. 11,590,229, or '229 patent, which we also believe Pfizer and Moderna's COVID-19 vaccines infringe upon. On February 15, 2023, we filed a motion with the court to add this patent to the existing cases against Pfizer and Moderna, and on April 26, 2023, the court held a hearing and denied Moderna's partial motion to dismiss those claims for sales under Section 1498(a), our motion to add the '229 patent to the then current lawsuits as well as a motion filed by Moderna to add certain invalidity arguments made by Pfizer in our case to supplement Moderna's invalidity arguments previously made.

On May 26, 2023, we filed additional lawsuits against Pfizer and Moderna in Delaware seeking damages for infringing the '229 patent. In addition to this patent, we added U.S. Patent Nos. 11,633,479 and 11,633,480 in the recently filed suits against both Pfizer and Moderna and also U.S. Patent No. 11,612,657 against Pfizer only.

On August 9, 2023, a Markman hearing was held in the U.S. District Court for the District of Delaware to consider the meaning of three disputed terms as used in the '933 and '979 patents. On August 21, 2023, the court issued an order construing two of the three terms, and deferred a ruling on the third term pending an evidentiary hearing, which was held on January 4, 2024 with the final ruling pending the outcome of an additional evidentiary hearing scheduled for July 11-12, 2024. Subsequently, we and Moderna jointly agreed to final judgment of non-infringement of two of our patents, and such judgment was entered by the court on August 30, 2023, and on September 7, 2023, we appealed the claim construction ruling to the Court of Appeals for the Federal Circuit in the initial lawsuit against Moderna. The claim construction ruling did not affect one of the patents in the lawsuit filed against Moderna on May 26, 2023, and that case is going forward on a schedule to be set by the court.

The two separate suits against Pfizer are ongoing subject to the ruling on the third claim term, and in September 2023, we and Pfizer agreed to consolidate the 2022 and 2023 lawsuits in one case, which will require moving the trial date from November 2024 to the first half of 2025, with the final schedule to be determined by the court.

Indemnifications

In connection with license agreements we may enter with companies to obtain rights to intellectual property, we may be required to indemnify such companies for certain damages arising in connection with the intellectual property rights licensed under the agreements. Under such agreements, we may be responsible for paying the costs of any litigation relating to the license agreements or the underlying intellectual property rights, including the costs associated with certain litigation regarding the licensed intellectual property. We are also a party to a number of agreements entered into in the ordinary course of business, which contain typical provisions that obligate us to indemnify the other parties to such agreements upon the occurrence of certain events, including litigation or other legal proceedings. In addition, we have agreed to indemnify our officers and directors for expenses, judgments, fines, penalties, excise taxes, and settlement amounts paid in connection with any threatened, pending or completed litigation proceedings, in which an officer or director was, is or will be involved as a party, on account of such person's status as an officer or director, or by reason of any action taken by the officer or director while acting in such capacity, subject to certain limitations. These indemnification costs are charged to selling, general and administrative expense.

Our maximum potential future liability under any such indemnification provisions is uncertain. We have determined that the estimated aggregate fair value of our potential liabilities under all such indemnification provisions is minimal and had not recorded any liability related to such indemnification provisions as of March 31, 2024.

ITEM 2. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

Overview

We are a global commercial-stage biopharmaceutical company developing novel therapeutics based on ribonucleic acid interference, or RNAi. RNAi is a naturally occurring biological pathway within cells for sequence-specific silencing and regulation of gene expression. By harnessing the RNAi pathway, we have developed a new class of innovative medicines, known as RNAi therapeutics. RNAi therapeutics are comprised of small interfering RNA, or siRNA, that function upstream of conventional medicines by potently silencing messenger RNA, or mRNA, that encode for proteins implicated in the cause or pathway of disease, thus preventing them from being made. We believe this is a revolutionary approach with the potential to transform the care of patients with rare and prevalent diseases. To date, our efforts to advance this revolutionary approach have yielded the approval of five first-in-class RNAi-based medicines, ONPATTRO[®] (patisiran), AMVUTTRA[®] (vutrisiran), GIVLAARI[®] (givosiran), OXLUMO[®] (lumasiran) and Leqvio[®] (inclisiran).

Our research and development strategy is to target genetically validated genes that have been implicated in the cause or pathway of human disease. We utilize a N-acetylgalactosamine (GalNAc) conjugate approach or lipid nanoparticle (LNP) to enable hepatic delivery of siRNAs. For delivery to the central nervous system, or CNS, and the eye (ocular delivery), we are utilizing an alternative conjugate approach based on a hexadecyl (C16) moiety as a lipophilic ligand. We are also advancing approaches for heart, skeletal muscle and adipose tissue delivery of siRNAs. Our focus is on clinical indications where there is a high unmet need, a genetically validated target, early biomarkers for the assessment of clinical activity in Phase 1 clinical studies, and a definable path for drug development, regulatory approval, patient access and commercialization.

In early 2021, we launched our *Amylam P⁵x25* strategy, which focuses on our planned transition to a top-tier biotech company by the end of 2025. With *Amylam P⁵x25*, we aim to deliver transformative rare, specialty and select prevalent disease medicines for patients around the world through sustainable innovation, while delivering exceptional financial performance.

We currently have five marketed products and more than ten clinical programs, including several in late-stage development, across rare, specialty and select prevalent indications.

ONPATTRO is approved by the United States Food and Drug Administration, or the FDA, for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis, or hATTR amyloidosis, in adults and has also been approved in the European Union, or EU, for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy, in Japan for the treatment of transthyretin, or TTR, type familial amyloidosis with polyneuropathy, and in multiple additional countries, including Brazil. In August 2022, we reported positive results from the APOLLO-B Phase 3 study of patisiran (the non-branded name of ONPATTRO) in patients with ATTR amyloidosis with cardiomyopathy, and in December 2022, we submitted a supplemental New Drug Application, or sNDA, to the FDA for patisiran as a potential treatment for the ATTR amyloidosis with cardiomyopathy. On September 13, 2023, the FDA's Cardiovascular and Renal Drugs Advisory Committee, or CRDAC, voted 9:3 that patisiran's benefits outweigh its risks for the treatment of transthyretin amyloidosis, or ATTR amyloidosis, with cardiomyopathy. Nevertheless, on October 6, 2023, the FDA issued a complete response letter, or CRL, indicating that evidence of clinical meaningfulness of patisiran was not established for ATTR amyloidosis with cardiomyopathy, and therefore the sNDA for patisiran could not be approved in its present form. The CRL did not identify any issues with respect to clinical safety, study conduct, drug quality or manufacturing. Patisiran remains under regulatory review with the Brazilian Health Regulatory Agency (ANVISA) for ONPATTRO for the treatment of ATTR amyloidosis with cardiomyopathy.

AMVUTTRA is approved in the U.S. for the treatment of hATTR amyloidosis with polyneuropathy in adults, in the EU and the United Kingdom, or UK, for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy, in Japan for the treatment of TTR type familial amyloidosis with polyneuropathy, and in multiple additional countries. Regulatory filings continue in other territories with submissions currently under review or planned for 2024 and beyond. We are currently conducting the HELIOS-B Phase 3 clinical trial of vutrisiran (the non-branded drug name for AMVUTTRA), which is investigating the potential of vutrisiran to treat the cardiac manifestations of disease in patients with ATTR amyloidosis with cardiomyopathy. Topline results from the HELIOS-B study are expected in late June or early July 2024.

GIVLAARI is approved in the U.S. for the treatment of adults with acute hepatic porphyria, or AHP, in the EU for the treatment of AHP in adults and adolescents aged 12 years and older, and in several other countries. Regulatory filings for givosiran (the non-branded drug name for GIVLAARI) in additional territories are pending or planned during 2024 and beyond.

OXLUMO is approved in the U.S. for the treatment of primary hyperoxaluria type 1, or PH1, to lower urinary and plasma oxalate levels in pediatric and adult patients, and in the EU and the UK for the treatment of PH1 in all age groups. OXLUMO has also been approved in several other countries and regulatory filings in additional territories are pending or planned during 2024 and beyond.

Leqvio (inclisiran), our fifth product, is being developed and commercialized by our collaborator Novartis AG, or Novartis, and has received marketing authorization from the European Commission, or EC, for the treatment of adults with

hypercholesterolemia or mixed dyslipidemia and from the FDA as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia, or HeFH, or clinical atherosclerotic cardiovascular disease, or ASCVD, who require additional lowering of low-density lipoprotein cholesterol, or LDL-C. In July 2023, the FDA approved an expanded indication for Leqvio to include treatment of adults with high LDL-C and who are at increased risk of heart disease. In the third quarter of 2023, Leqvio was approved in China and Japan, and as of the end of March 2024, Leqvio had been approved in more than 90 countries.

In addition to our marketed products, we have multiple late-stage investigational programs advancing toward potential commercialization. These programs include our wholly owned programs: vutrisiran (the non-branded drug name for AMVUTTRA) for the treatment of ATTR amyloidosis (wild-type or hereditary) with cardiomyopathy; as well as fitusiran for the treatment of hemophilia, which is being advanced by our collaborator Genzyme Corporation, a Sanofi Company, or Sanofi; and cemdisiran for the treatment of complement-mediated diseases, where our collaborator Regeneron Pharmaceuticals, Inc., or Regeneron, is advancing cemdisiran in combination with pozelimab in Phase 3 studies in myasthenia gravis and paroxysmal nocturnal hemoglobinuria.

As part of our *Amylam P⁵x25* strategy, we have multiple drivers of future growth, including the development of transformative medicines to treat prevalent disease. In addition to Leqvio, we are advancing zilebesiran, an investigational, subcutaneously administered RNAi therapeutic targeting angiotensinogen, or AGT, in development for the treatment of hypertension. In 2023, we entered into a Collaboration and License Agreement, or the Roche Collaboration and License Agreement, with F. Hoffmann-La Roche Ltd. and Genentech, Inc. or, collectively, Roche, pursuant to which we established a worldwide, strategic collaboration for the joint development and commercialization of zilebesiran. In March 2024, we reported positive topline results from our KARDIA-2 clinical trial, which is designed to evaluate the safety and efficacy of zilebesiran administered biannually as a concomitant therapy in patients whose blood pressure is not adequately controlled by a standard of care antihypertensive medication. In April 2024, we dosed the first patient in our KARDIA-3 clinical trial, which is designed to evaluate the efficacy and safety of zilebesiran used as an add-on therapy in adult patients with high cardiovascular risk and uncontrolled hypertension despite treatment with two to four standard of care antihypertensive medications.

We are also advancing mivelsiran (formerly ALN-APP), an investigational RNAi therapeutic targeting amyloid precursor protein in development for the treatment of Alzheimer's disease and cerebral amyloid angiopathy. In 2023, we reported positive interim results from the ongoing single ascending dose part of the Phase 1 study of mivelsiran in patients with early-onset Alzheimer's disease. These results establish the first human translation of our proprietary C16-siRNA conjugate platform for CNS delivery and are the first clinical demonstration of gene silencing in the human brain using an RNAi therapeutic.

In further support of our *Amylam P⁵x25* strategy and in view of our evolving risk profile, we remain focused on the continued evolution of our global infrastructure, including key objectives such as optimizing our global structure for execution in key markets, enhancing performance consistent with our values, and continuing to strengthen our culture. We continue to build our global compliance program to drive its evolution and enhancement in view of the *Amylam P⁵x25* strategy. Building from our global Code of Business Conduct and Ethics, our compliance program is designed to empower our employees and those with whom we work to execute on our strategy consistent with our values and in compliance with applicable laws and regulations, and to mitigate risk. Comprised of components such as risk assessment and monitoring; policies, procedures, and guidance; training and communications; dedicated resources; and systems and processes supporting activities such as third party relationships and investigations and remediation; our program and related controls are built to enhance our business processes, structures, and controls across our global operations, and to empower ethical decision making.

Based on our expertise in RNAi therapeutics and broad intellectual property estate, we have formed collaborations with leading pharmaceutical and life sciences companies to support our development and commercialization efforts, including Roche, Regeneron, Sanofi, and Novartis (which acquired our collaborator The Medicines Company, or MDCO, in 2020).

We have incurred significant losses since we commenced operations in 2002 and as of March 31, 2024, we had an accumulated deficit of \$7.08 billion. Historically, we have generated losses principally from costs associated with research and development activities, acquiring, filing and expanding intellectual property rights, and selling, general and administrative costs. As a result of planned expenditures for research and development activities relating to our research platform, our drug development programs, including clinical trial and manufacturing costs, the establishment of late-stage clinical and commercial capabilities, including global commercial operations, continued management and growth of our patent portfolio, collaborations and general corporate activities, we expect to incur additional operating losses. While we believe 2019 was our peak operating loss year, we expect to continue to incur annual operating losses, and will require substantial resources over the next several years as we expand our efforts to discover, develop and commercialize RNAi therapeutics, and aim to achieve financial self-sustainability by the end of 2025. We anticipate that our operating results will continue to fluctuate for the foreseeable future, therefore, period-to-period comparisons should not be relied upon as predictive of the results in future periods.

We currently have programs focused on a number of therapeutic areas and, as of March 31, 2024, we generate worldwide product revenues from four commercialized products, ONPATTRO, AMVUTTRA, GIVLAARI and OXLUMO, primarily in the U.S. and Europe. However, our ongoing development efforts may not be successful and we may not be able to commence sales of any other products and/or successfully market and sell our existing commercialized products or any other approved

products in the future. A substantial portion of our total revenues in recent years has been derived from collaboration revenues from collaborations with Roche, Regeneron and Novartis. In addition to revenues from the commercial sales of our approved products and potentially from sales of future products, we expect our sources of potential funding for the next several years to continue to be derived in part from existing and new strategic collaborations. Such collaborations include, or may include in the future, license and other fees, funded research and development, milestone payments and royalties on product sales by our licensors, including royalties on sales of Leqvio made by our collaborator Novartis, as well as proceeds from the sale of equity or debt.

Research and Development

Since our inception, we have focused on drug discovery and development programs. Research and development expenses represent a substantial percentage of our total operating expenses, as reflected by our broad pipeline of clinical development programs, which includes multiple programs in late-stage development.

Our Product Pipeline

Our broad pipeline, including five approved products and multiple late and early-stage investigational RNAi therapeutics, addresses unmet needs in several disease areas, and spans indications in rare, specialty and select prevalent diseases. We describe our commercial and clinical-stage pipeline in more detail below. The investigational therapeutics described below are in various stages of clinical development and the scientific information included about these therapeutics is preliminary and investigative. None of these investigational therapeutics have been approved by the FDA, EMA, or any other health authority and no conclusions can or should be drawn regarding the safety or efficacy of these investigational therapeutics.

The table below represents our commercial products and late- and early-stage development programs as of May 1, 2024.

PRODUCT	DISEASE	PIPELINE			
		PHASE 1	PHASE 2	PHASE 3	COMMERCIAL
ONPATTRO® (patisiran)	hATTR Amyloidosis with Polyneuropathy (PN)	██████████	██████████	██████████	██████████
AMVUTTRA® (vutrisiran)	hATTR Amyloidosis with Polyneuropathy (PN)	██████████	██████████	██████████	██████████
GIVLAARI® (givosiran)	Acute Hepatic Porphyria (AHP)	██████████	██████████	██████████	██████████
OXLUMO® (lumasiran)	Primary Hyperoxaluria Type 1 (PH1)	██████████	██████████	██████████	██████████
Leqvio® (inclisiran)	Hypercholesterolemia**	██████████	██████████	██████████	██████████
Vutrisiran	ATTR Amyloidosis with Cardiomyopathy (CM)	██████████	██████████	██████████	
Fitusiran	Hemophilia**	██████████	██████████	██████████	
Cemdisiran (+/- Pozelimab)	Myasthenia Gravis**	██████████	██████████	██████████	
Cemdisiran (+/- Pozelimab)	Paroxysmal Nocturnal Hemoglobinuria**	██████████	██████████	██████████	
Zilebesiran	Hypertension [⊠]	██████████	██████████		
ALN-HSD	NASH**	██████████	██████████		
Elebsiran (ALN-HBV02/VIR-2218)	Hepatitis B Virus Infection [‡]	██████████	██████████		
Elebsiran (ALN-HBV02/VIR-2218)	Hepatitis D Virus Infection [‡]	██████████	██████████		
Mivelsiran (ALN-APP)	Cerebral Amyloid Angiopathy (CAA)*	██████████	██████████		
ALN-TTRsc04	ATTR Amyloidosis	██████████			
Mivelsiran (ALN-APP)	Alzheimer's Disease*	██████████			
ALN-KHK	Type 2 Diabetes Mellitus	██████████			
ALN-BCAT	Hepatocellular Carcinoma	██████████			
ALN-PNP	NASH [‡]	██████████			

* Collaborated, Alnylam-led with profit split

‡ Collaborator-led with Alnylam option for profit split

** Out-licensed with milestones and/or royalties

† Collaborator-led with profit split

⊠ Collaborated, Alnylam-led development with US profit split and milestones/royalties ex-US

During the first quarter of 2024 and recent period, we reported the following updates from our commercially approved products and our late-stage clinical programs:

Commercial

Total TTR: ONPATTRO & AMVUTTRA

- We achieved global net product revenues for ONPATTRO and AMVUTTRA for the first quarter of 2024 of \$69.2 million and \$195.2 million, respectively.

Total Rare: GIVLAARI & OXLUMO

- We achieved global net product revenues for GIVLAARI and OXLUMO for the first quarter of 2024 of \$58.1 million and \$42.6 million, respectively.

Late-Stage Clinical Development

- Announced updates to the statistical analysis plan for the HELIOS-B Phase 3 study of vutrisiran in patients with ATTR amyloidosis with cardiomyopathy, including adjustments to the primary and secondary endpoints and analysis period. Topline results remain on track to be reported in late June or early July.
- We continued to advance zilebesiran, an investigational RNAi therapeutic in development to treat hypertension in patients at high cardiovascular risk:
 - Reported positive results from the KARDIA-2 Phase 2 dose-ranging study of zilebesiran added to standard-of-care antihypertensives in patients with inadequately controlled hypertension.
 - Initiated the global KARDIA-3 Phase 2 study of zilebesiran in adult patients with high cardiovascular risk and uncontrolled hypertension despite treatment with two to four standard of care antihypertensive medications

There is a risk that any drug discovery or development program may not produce revenue for a variety of reasons, including the possibility that we will not be able to adequately demonstrate the safety and effectiveness of the product candidate or obtain approval or the desired labeling for the product candidate from regulatory authorities. Moreover, there are uncertainties specific to any new field of drug discovery, including RNAi. The success of ONPATTRO, AMVUTTRA, GIVLAARI, OXLUMO or any other product candidate we develop is highly uncertain. Due to the numerous risks associated with developing drugs, we cannot reasonably estimate or know the nature, timing and estimated costs of the efforts necessary to complete the development of any potential product candidate or indication, or the period, if any, in which material net cash inflows will commence from any approved product or indication. Any failure to complete any stage of the development of any potential products or any approved product for an expanded indication in a timely manner or successfully launch, market and sell any of our commercially approved products, could have a material adverse effect on our operations, financial position and liquidity. A discussion of some of the risks and uncertainties associated with completing our research and development programs within the planned timeline, or at all, and the potential consequences of failing to do so, are set forth in Part II, Item 1A below under the heading “Risk Factors.”

Strategic Collaborations

Our business strategy is to develop and commercialize a broad pipeline of RNAi therapeutic products directed towards transformative rare, specialty and select prevalent diseases. As part of this strategy, we have entered into, and may in the future enter into additional, collaboration and licensing agreements as a means of obtaining resources, capabilities and funding to advance our investigational RNAi therapeutic programs.

Below is a brief description of certain of our key collaborations.

Roche. In July 2023, we entered into the Roche Collaboration and License Agreement, pursuant to which we and Roche established a worldwide, strategic collaboration for the joint development of pharmaceutical products containing zilebesiran. Under the Roche Collaboration and License Agreement, we granted to Roche (i) co-exclusive rights to develop and commercialize zilebesiran in the U.S. and (ii) exclusive rights to develop and commercialize zilebesiran outside of the U.S. Roche made an upfront payment of \$310.0 million. In April 2024, we achieved the development milestone associated with the first patient dosed in the KARDIA-3 Phase 2 trial, entitling us to receive a \$65.0 million development milestone payment from Roche. In addition, we will be eligible to receive up to an additional \$2.45 billion in contingent payments based on the achievement of specified development, regulatory and sales-based milestones. We will be responsible for forty percent (40%) and Roche will be responsible for the remaining sixty percent (60%) of development costs incurred in the conduct of development activities that support regulatory approval of zilebesiran globally. We and Roche will share equally (50/50) all costs incurred in connection with development activities that are conducted primarily to support regulatory approval of zilebesiran in the U.S., and Roche will be solely responsible for costs incurred in connection with commercialization of zilebesiran outside of the U.S. and will pay us tiered, low double digit royalties based on net sales of zilebesiran on a country-

by-country basis outside of the U.S. during the royalty term. We and Roche will share equally (50/50) profits and losses (including commercialization costs) of zilebesiran in the U.S.

Regeneron. In April 2019, we entered into a global, strategic collaboration with Regeneron to discover, develop and commercialize RNAi therapeutics for a broad range of diseases by addressing therapeutic targets expressed in the eye and CNS, in addition to a select number of targets expressed in the liver, which we refer to as the Regeneron Collaboration. The Regeneron Collaboration is governed by a Master Agreement, referred to as the Regeneron Master Agreement, which became effective in May 2019. In August 2019, we and Regeneron entered into (i) a co-co collaboration agreement covering the continued development of cemdisiran, our C5 siRNA currently Phase 3 ready for IgAN as a monotherapy and (ii) a license agreement covering evaluation of anti-C5 antibody-siRNA combinations for C5 complement-mediated diseases including evaluating the combination of Regeneron's pozelimab and cemdisiran.

Under the terms of the Regeneron Collaboration, we are working exclusively with Regeneron to discover RNAi therapeutics for eye and CNS diseases for an initial five-year research period, subject to extension for up to an additional five years, or the Initial Research Term. The Regeneron Collaboration also covers a select number of RNAi therapeutic programs designed to target genes expressed in the liver, including our previously-announced collaboration with Regeneron to identify RNAi therapeutics for the chronic liver disease NASH. We retain broad global rights to all of our liver-directed clinical and pre-clinical pipeline programs that have not been collaborated.

Regeneron leads development and commercialization for all programs targeting eye diseases (subject to limited exceptions), entitling us to certain potential milestone and royalty payments pursuant to the terms of a license agreement, the form of which has been agreed upon by the parties. We and Regeneron are alternating leadership on CNS and liver programs, with the lead party retaining global development and commercial responsibility.

We and Regeneron plan to advance programs directed to up to 30 targets under the Regeneron Collaboration during the Initial Research Term. In July 2020, Regeneron exercised its co-development/co-commercialization option on mivelsiran, an investigational RNAi therapeutic in development for the treatment of hereditary cerebral amyloid angiopathy and autosomal dominant Alzheimer's Disease, which we are leading. We are also advancing multiple other programs with Regeneron.

Sanofi. We formed a broad strategic alliance with Sanofi in 2014. In January 2018, we and Sanofi amended our 2014 collaboration and entered into the Exclusive License Agreement, referred to as the Exclusive TTR License, under which we have the exclusive right to pursue the further global development and commercialization of all TTR products, including ONPATTRO, AMVUTTRA and any back-up products, and the ALN-AT3 Global License Terms, referred to as the AT3 License Terms, under which Sanofi has the exclusive right to pursue the further global development and commercialization of fitusiran and any back-up products. In April 2019, we and Sanofi agreed to further amend the 2014 Sanofi collaboration to conclude the research and option phase and to amend and restate the AT3 License Terms to modify certain of the business terms. The material collaboration terms for fitusiran were unchanged. Under the amended and restated AT3 License Terms, we are eligible to receive tiered royalties of 15% to 30% based on global annual net sales of fitusiran by Sanofi, its affiliates and its sublicensees.

Novartis. In February 2013, we entered into an exclusive, worldwide license with MDCO (acquired by Novartis AG in January 2020) pursuant to which MDCO was granted the right to develop, manufacture and commercialize RNAi therapeutics targeting proprotein convertase subtilisin/kexin type 9 for the treatment of hypercholesterolemia and other human diseases, including Leqvio.

We also have entered into license agreements to obtain rights to intellectual property in the field of RNAi. In addition, because delivery of RNAi therapeutics has historically been an important objective of our research activities, we have entered into various collaboration and licensing arrangements with other companies and academic institutions to gain access to delivery technologies, including various LNP delivery technologies, and we may enter into such agreements in the future to gain access to products or technologies.

Critical Accounting Policies and Estimates

Our critical accounting policies are described in the "Management's Discussion and Analysis of Financial Condition and Results of Operations" section of our Annual Report on Form 10-K for the year ended December 31, 2023, which we filed with the SEC on February 15, 2024. There have been no significant changes to our critical accounting policies since the beginning of this fiscal year.

Results of Operations

The following data summarizes the results of our operations:

(In thousands, except percentages)	Three Months Ended March 31,			
	2024	2023	\$ Change	% Change
Total revenues	\$ 494,333	\$ 319,290	\$ 175,043	55 %
Operating costs and expenses	\$ 537,768	\$ 469,097	\$ 68,671	15 %
Loss from operations	\$ (43,435)	\$ (149,807)	\$ 106,372	(71)%
Net loss	\$ (65,935)	\$ (174,101)	\$ 108,166	(62)%

Discussion of Results of Operations

Revenues

Total revenues consist of the following:

(In thousands, except percentages)	Three Months Ended March 31,			
	2024	2023	\$ Change	% Change
Net product revenues	\$ 365,163	\$ 276,328	\$ 88,835	32 %
Net revenues from collaborations	118,548	36,462	82,086	225 %
Royalty revenue	10,622	6,500	4,122	63 %
Total	\$ 494,333	\$ 319,290	\$ 175,043	55 %

Net Product Revenues

Net product revenues consist of the following, by product and region:

(In thousands, except percentages)	Three Months Ended March 31,			
	2024	2023	\$ Change	% Change
ONPATTRO				
United States	\$ 16,539	\$ 29,817	\$ (13,278)	(45)%
Europe	44,690	59,678	(14,988)	(25)%
Rest of World	7,988	12,998	(5,010)	(39)%
Total	69,217	102,493	(33,276)	(32)%
AMVUTTRA				
United States	130,238	79,013	51,225	65 %
Europe	43,733	6,768	36,965	*
Rest of World	21,270	15,987	5,283	33 %
Total	195,241	101,768	93,473	92 %
GIVLAARI				
United States	38,731	30,291	8,440	28 %
Europe	15,315	14,471	844	6 %
Rest of World	4,010	3,144	866	28 %
Total	58,056	47,906	10,150	21 %
OXLUMO				
United States	13,332	9,057	4,275	47 %
Europe	21,427	13,309	8,118	61 %
Rest of World	7,890	1,795	6,095	340 %
Total	42,649	24,161	18,488	77 %
Total net product revenues	\$ 365,163	\$ 276,328	\$ 88,835	32 %

* Indicates the percentage change period over period is greater 500%.

Net product revenues increased during the three months ended March 31, 2024, as compared to the same periods in 2023, due to strong growth from AMVUTTRA driven by increased patient demand, as well as increased patients on GIVLAARI and OXLUMO therapies.

Net Revenues from Collaborations and Royalty Revenue

Net revenues from collaborations and royalty revenue consist of the following:

(In thousands, except percentages)	Three Months Ended March 31,			
	2024	2023	\$ Change	% Change
Roche	\$ 74,680	\$ —	\$ 74,680	N/A
Regeneron Pharmaceuticals	26,764	19,990	6,774	34 %
Novartis AG	14,516	14,933	(417)	(3)%
Other	2,588	1,539	1,049	68 %
Total net revenues from collaborations	\$ 118,548	\$ 36,462	\$ 82,086	225 %
Royalty revenue	\$ 10,622	\$ 6,500	\$ 4,122	63 %

Net revenues from collaborations increased during the three months ended March 31, 2024, as compared to the same period in 2023, due to revenue recognized under our Collaboration and License Agreement with Roche, including \$65.0 million of milestone revenue associated with dosing the first patient in the zilebesiran KARDIA-3 clinical trial, and increased revenue recognized in connection with our Regeneron Collaboration as a result of an increase in activities under our research services arrangement and licensed programs.

Royalty revenue increased during the three months ended March 31, 2024, as compared to the same period in 2023, due to increased royalties earned from global net sales of Leqvio by our collaborator, Novartis.

Recognition of our combined net revenues from collaborations and royalty revenue is dependent on a variety of factors including the level of work reimbursed by collaborators, achievement of milestones under our collaboration agreements, and royalties associated with sales of Leqvio. We expect net revenues from collaborations and royalty revenue to decrease in 2024, as compared to 2023, primarily driven by a reduction in the revenues recognized under our Collaboration and License Agreement with Roche. We expect our royalty revenues will increase in 2024, as compared to 2023, due to the continued growth of royalties earned from global net sales of Leqvio by our collaborator, Novartis.

Operating Costs and Expenses

Operating costs and expenses consist of the following:

(In thousands, except percentages)	Three Months Ended March 31,			
	2024	2023	\$ Change	% Change
Cost of goods sold	\$ 54,613	\$ 41,432	\$ 13,181	32 %
<i>Cost of goods sold as a percentage of net product revenues</i>	<i>15.0 %</i>	<i>15.0 %</i>		
Cost of collaborations and royalties	11,363	13,437	(2,074)	(15)%
Research and development	260,995	230,569	30,426	13 %
Selling, general and administrative	210,797	183,659	27,138	15 %
Total	\$ 537,768	\$ 469,097	\$ 68,671	15 %

Cost of goods sold

Cost of goods sold as a percentage of net product revenues was consistent during the three months ended March 31, 2024, as compared to the same period in 2023, primarily due to increased royalties related to higher AMVUTTRA sales volume, partially offset by one-time favorability attributed to reduced ONPATTRO manufacturing cancellation fees.

We expect our cost of goods sold will increase during 2024, as compared to 2023, primarily as a result of an expected increase in net product sales as well as increased royalties.

Cost of collaborations and royalties

Cost of collaborations and royalties decreased during the three months ended March 31, 2024, as compared to the same period in 2023, primarily due to decreased demand of GalNAc material supplied to our collaborators in support of certain product manufacturing as our collaborators transition to producing the material independently.

We expect cost of collaborations and royalties will continue to decrease during 2024, as compared to 2023, as a result of our collaborators transitioning to produce GalNAc independently.

Research and development

Research and development expenses consist of the following:

(In thousands, except percentages)	Three Months Ended March 31,			
	2024	2023	\$ Change	% Change
Clinical research and outside services	\$ 125,510	\$ 111,597	\$ 13,913	12 %
Compensation and related	77,209	64,720	12,489	19 %
Occupancy and all other costs	39,061	38,020	1,041	3 %
Stock-based compensation	19,215	16,232	2,983	18 %
Total	\$ 260,995	\$ 230,569	\$ 30,426	13 %

For the three months ended March 31, 2024, the increase in research and development expenses, as compared to the same period in 2023, was primarily due to the following:

- increased clinical research expenses primarily associated with zilebesiran in the KARDIA-2 and KARDIA-3 clinical studies;
- increased expenses associated with our HELIOS-B study primarily driven by increased costs and fees leading up to the topline data readout in late June or early July 2024;
- increased costs associated with our preclinical activities, specifically our CNS programs, as we continue to expand our R&D pipeline; and
- increased compensation and related expenses as a result of increased headcount to support our R&D pipeline and development expenses.

During the three months ended March 31, 2024 and 2023, in connection with advancing activities under our collaboration agreements, we incurred research and development expenses, primarily related to external development and clinical services, including the manufacture of clinical product.

The following table summarizes research and development expenses incurred, for which we recognize net revenue, that are directly attributable to our collaboration agreements, by collaborator:

(In thousands)	Three Months Ended March 31,	
	2024	2023
Roche	\$ 18,081	\$ —
Regeneron Pharmaceuticals	18,703	19,119
Other	2,813	798
Total	\$ 39,597	\$ 19,917

Selling, general and administrative

Selling, general and administrative expenses consist of the following:

(In thousands, except percentages)	Three Months Ended March 31,			
	2024	2023	\$ Change	% Change
Compensation and related	\$ 91,209	\$ 74,326	\$ 16,883	23 %
Consulting and professional services	56,759	50,688	6,071	12 %
Occupancy and all other costs	36,697	34,930	1,767	5 %
Stock-based compensation	26,132	23,715	2,417	10 %
Total	\$ 210,797	\$ 183,659	\$ 27,138	15 %

For the three months ended March 31, 2024, the increase in selling, general and administrative expenses, as compared to the same period in 2023, was primarily due to increased marketing investment associated with promotion of our TTR therapies and increased headcount and other investments supporting our strategic growth.

We expect that research and development expenses combined with selling, general and administrative expenses will continue to increase during 2024, as compared to 2023, as we continue to advance and develop our platform and pipeline, advance our product candidates, including collaborated programs, into later-stage development, prepare regulatory submissions and continue to build-out our global commercial and compliance infrastructure as well as launch our commercial products into additional markets, assuming regulatory approvals. However, we expect that certain expenses will be variable depending on the timing of manufacturing batches, clinical trial enrollment and results, regulatory review of our product candidates and programs, and stock-based compensation expenses due to our determination regarding the probability of vesting for performance-based awards.

Other (Expense) Income

Other (expense) income consists of the following:

(In thousands, except percentages)	Three Months Ended March 31,			
	2024	2023	\$ Change	% Change
Interest expense	\$ (35,253)	\$ (28,955)	\$ (6,298)	22 %
Interest income	29,645	18,655	10,990	59 %
Other expense, net				
Realized and unrealized loss on marketable equity securities	78	(2,267)	2,345	(103)%
Change in fair value of development derivative liability	(8,586)	(6,471)	(2,115)	33 %
Other	(6,036)	(3,517)	(2,519)	72 %
Total	\$ (20,152)	\$ (22,555)	\$ 2,403	(11)%

Total other expense decreased during the three months ended March 31, 2024, as compared to the same period in 2023, primarily due to increased interest income driven by higher market interest rates on our marketable debt securities, partially offset by increased interest expense as a result of interest accretion on larger debt balances in 2024, as compared to 2023, specifically related to the liability related to the sale of future royalties.

Liquidity and Capital Resources

The following table summarizes our cash flow activities:

(In thousands)	Three Months Ended March 31,	
	2024	2023
Net cash provided by (used in):		
Operating activities	\$ (81,515)	\$ (166,475)
Investing activities	\$ (67,620)	\$ (76,217)
Financing activities	\$ 28,911	\$ 46,371

Operating activities

Net cash used in operating activities decreased during the three months ended March 31, 2024, compared to the same period in 2023, primarily due to stronger cash receipts from increased product sales in addition to decreased cash disbursements related to working capital payments.

Investing activities

Net cash used in investing activities decreased during the three months ended March 31, 2024, compared to the same period in 2023, primarily due to net activities related to our marketable debt securities.

Financing activities

Net cash provided by financing activities decreased during the three months ended March 31, 2024, compared to the same period in 2023, primarily due to decreased net proceeds from the issuance of common stock in connection with stock option exercises.

Additional Capital Requirements

We currently have programs focused in many therapeutic areas and, as of March 31, 2024, have received regulatory approval and commercially launched four products. However, our ongoing development efforts may not be successful and we may not be able to commence sales of any other products or successfully expand the indications for our approved products, including AMVUTTRA, in the future. In addition, we anticipate that we will continue to generate losses as a result of planned expenditures for research and development activities relating to our research platform, our drug development programs, including clinical trial and manufacturing costs, the establishment of late-stage clinical, manufacturing, commercial and compliance capabilities, including global operations, continued management and growth of our intellectual property including our patent portfolio, collaborations and general corporate activities.

Our expected working and other capital requirements are described in our 2023 Annual Report on Form 10-K in "Part II, Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations." As of March 31, 2024, other than the changes disclosed in the "Notes to Condensed Consolidated Financial Statements" and "Liquidity and Capital Resources" section in this Quarterly Report on Form 10-Q, there have been no other material changes to our expected working and other capital requirements as described in our 2023 Annual Report on Form 10-K.

Based on our current operating plan, we believe that our cash, cash equivalents and marketable securities as of March 31, 2024, together with the cash we expect to generate from product sales and under our current alliances, will be sufficient to satisfy our near-term capital and operating needs for at least the next 12 months from the filing date of this Quarterly Report on Form 10-Q. However, due to numerous factors described in more detail under the caption Part II, Item 1A, “Risk Factors” of this Quarterly Report on Form 10-Q, we may require significant additional funds earlier than we currently expect in order to continue to commercialize our approved products, and to develop, conduct clinical trials for, manufacture and, if approved, commercialize additional product candidates.

ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

Financial market risks related to interest rates are described in our Annual Report on Form 10-K for the year ended December 31, 2023. As of March 31, 2024, there have been no significant changes to the financial market risks described as of December 31, 2023. We do not currently anticipate any other near-term changes in the nature of our financial market risk exposures or in management’s objectives and strategies with respect to managing such exposures.

ITEM 4. CONTROLS AND PROCEDURES

Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer (principal executive officer) and executive vice president, Chief Financial Officer (principal financial officer), evaluated the effectiveness of our disclosure controls and procedures as of March 31, 2024. The term “disclosure controls and procedures,” as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC’s rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company’s management, including its principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of March 31, 2024, our Chief Executive Officer and executive vice president, Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Changes in Internal Control

There were no changes in our internal control over financial reporting during the quarter ended March 31, 2024 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

For a discussion of material pending legal proceedings, please read Note 13, Commitments and Contingencies, to our condensed consolidated financial statements included in Part I, Item I, “Financial Statements (Unaudited),” of this Quarterly Report on Form 10-Q, which is incorporated into this item by reference.

ITEM 1A. RISK FACTORS

Investing in our securities involves a high degree of risk. You should carefully consider the following risk factors in addition to the other information set forth or incorporated by reference in this Quarterly Report on Form 10-Q, including our condensed consolidated financial statements and the related notes and “Management’s Discussion of Financial Condition and Results of Operations,” in evaluating our company and our business. If any of the following risks, or any additional risk not currently known to us or that we currently deem immaterial, actually occurs, our business, prospects, operating result or financial condition could be materially and adversely affected. In these circumstances, the trading price of our common stock could decline, and you may lose all or part of your investment.

SUMMARY OF MATERIAL RISKS ASSOCIATED WITH OUR BUSINESS

Our business is subject to numerous risks and uncertainties, discussed in more detail in the following section. These risks include, among others, the following key risks:

Business Related Risks – Risks Related to Our Financial Results

- The marketing and sale of our approved products or any future products may be unsuccessful or less successful than anticipated and we may be unable to expand the approved indications for AMVUTTRA.
- We have a history of losses and may never become and remain profitable.
- We will require substantial funds to continue our research, development and commercialization activities.
- Any negative developments related to Leqvio could have a material adverse effect on our receipt of future royalties and milestone payments.

Risks Related to Our Dependence on Third Parties

- We may be unable to maintain existing or enter into new collaborations with other companies that can provide business and scientific capabilities and funds for the development and commercialization of certain of our product candidates.
- If any collaborator materially amends, terminates or fails to perform its obligations under agreements with us, the development and commercialization of certain of our product candidates could be delayed or terminated.
- We expect to continue to grow our manufacturing capabilities and resources and we must incur significant costs to develop this expertise and/or rely on third parties to manufacture our products.
- We rely on third parties to conduct our clinical trials, and if such third parties fail to fulfill their obligations, our development plans may be adversely affected.

Risks Related to Managing Our Operations

- If we are unable to attract and retain qualified key management and scientists, development, medical and commercial staff, consultants and advisors, our ability to implement our business plan may be adversely affected.
- We may have difficulty expanding our operations successfully as we continue our evolution from a U.S.- and Europe-based company primarily involved in discovery, pre-clinical testing and clinical development into a global company that develops and commercializes multiple drugs in multiple geographies including Asia, Latin America and the Middle East.

Industry Related Risks – Risks Related to Development, Clinical Testing and Regulatory Approval of Our Product Candidates and the Commercialization of Our Approved Products

- Any product candidate we or our collaborators develop may fail in development or be delayed to a point where such product candidate does not become commercially viable.
- We or our collaborators may be unable to obtain U.S. or foreign regulatory approval for our or our collaborated product candidates, and, as a result, we or our collaborators may be unable to commercialize such product candidates.
- Even if we or our collaborators obtain regulatory approvals, our products will be subject to ongoing regulatory oversight.

- We may incur significant liability if enforcement authorities allege or determine that we are engaging in commercial activities with respect to our unapproved product candidates or promoting our commercially approved products in a way that violates applicable regulations.
- Even if we or our collaborators receive regulatory approval to market our product candidates, the market may not be receptive to such product candidates upon their commercial introduction, which could prevent us from becoming profitable.
- We are a multi-product commercial company and expect to continue to invest significant financial and management resources to continue to build our marketing, sales, market access and distribution capabilities and further establish our global infrastructure, and our efforts may not be successful.
- Any products we currently market or may develop in the future may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, thereby harming our business.

Risks Related to Patents, Licenses and Trade Secrets

- If we are not able to obtain and enforce patent protection for our discoveries, our ability to develop and commercialize our product candidates will be harmed.
- We license patent rights from third-party owners. If such owners do not properly or successfully obtain, maintain or enforce the patents underlying such licenses, our competitive position may be harmed.
- Other companies or organizations may challenge our patent rights or may assert patent rights that prevent us from developing and commercializing our products.
- If we become involved in intellectual property litigation or other proceedings related to a determination of rights, including our ongoing patent infringement litigation against Pfizer, Inc., or Pfizer, and Moderna, Inc., or Moderna, we could incur substantial costs and expenses, and in the case of such litigation or proceedings against us, substantial liability for damages or be required to stop our product development and commercialization efforts.
- If we fail to comply with our obligations under any licenses or related agreements, we may be required to pay damages and could lose license or other rights that are necessary for developing, commercializing and protecting our ribonucleic acid interference, or RNAi, technology.

Risks Related to Competition

- The pharmaceutical market is intensely competitive. If we or our collaborators are unable to compete effectively with existing drugs, new treatment methods and new technologies, we or our collaborators may be unable to commercialize successfully any drugs that we or our collaborators develop.
- We and our collaborators face competition from other companies that are working to develop novel drugs and technology platforms using technology similar to ours, as well as from companies utilizing emerging technologies.

Risks Related to Our Common Stock

- Our stock price has been and may in the future be volatile, and an investment in our common stock could suffer a decline in value.
- We expect that results from our and our collaborators' clinical development activities and the clinical development activities of our competitors will continue to be released periodically and may result in significant volatility in the price of our common stock.

Risks Related to Our Convertible Notes

- We may not have sufficient cash flow from our business to pay our indebtedness.
- We may not have the ability to raise the funds necessary to settle for cash conversions of our 1% Convertible Senior Notes due 2027, or the Notes, or to repurchase the Notes for cash upon a fundamental change.
- The conditional conversion feature of the Notes, if triggered, may adversely affect our liquidity.

Risks Related to Our Business

Risks Related to Our Financial Results

The marketing and sale of our approved products or any future products may be unsuccessful or less successful than anticipated, and we may be unable to expand the approved indications for certain of our commercial products, including AMVUTTRA.

Although we have commercially launched four products, we cannot predict whether we will successfully market and sell our approved products, or successfully expand the approved indications of certain of our commercial products, including

AMVUTTRA. For example, in August and September 2022, we reported positive safety and efficacy results from the APOLLO-B Phase 3 clinical trial of patisiran, which was designed and powered to evaluate the effects of patisiran on functional capacity and quality of life in patients with ATTR amyloidosis with cardiomyopathy. While we believe that the APOLLO-B results after 12 months validate the therapeutic hypothesis of RNAi therapeutics targeting TTR as potential treatment for patients with ATTR amyloidosis with cardiomyopathy, in October 2023, the FDA issued a CRL for our sNDA, for patisiran for the treatment of ATTR amyloidosis with cardiomyopathy, indicating that the clinical meaningfulness of patisiran's treatment effects for ATTR amyloidosis with cardiomyopathy had not been established, and therefore, the sNDA could not be approved in its submitted form.

To execute our business plan of building a profitable, top-tier biotech company by the end of 2025 and achieving our *Alnylam P⁵x25* strategy and the metrics associated with such strategy, in addition to successfully marketing, selling and expanding the approved indications of our approved products, we will need to successfully:

- execute product development activities and continue to leverage new technologies related to both RNAi and to the delivery of siRNAs to the relevant tissues and cells, including the liver, CNS, eye, lung, adipose and muscle;
- build and maintain a strong intellectual property portfolio;
- gain regulatory acceptance for the development and commercialization of our product candidates and successfully market our approved products, as well as any other products we commercialize;
- attract and retain customers for our products;
- enter into and maintain successful collaborations; and
- manage our spending as costs and expenses increase due to clinical trials, regulatory approvals and commercialization.

If we are unsuccessful in accomplishing the objectives set forth above, we may not be able to develop product candidates, successfully commercialize our approved products or any future products, raise capital, if needed, repay our indebtedness, achieve financial self-sustainability or continue our operations.

We have a history of losses and may never become and remain profitable.

We have experienced significant operating losses since our inception. As of March 31, 2024, we had an accumulated deficit of \$7.08 billion. Although to date we have launched four products in the U.S., EU and various other countries globally, and expect to launch our commercially approved products in additional countries during 2024 and beyond, we may never attain profitability or positive cash flow from operations. For the three months ended March 31, 2024, we recognized \$365.2 million in net product revenues from sales of ONPATTRO, AMVUTTRA, GIVLAARI and OXLUMO. While we believe 2019 was our peak operating loss year, we expect to continue to incur annual operating losses, and will require substantial resources over the next several years as we expand our efforts to discover, develop and commercialize RNAi therapeutics, and aim to achieve financial self-sustainability by the end of 2025. While we believe our current cash, cash equivalents and marketable equity and debt securities, as well as the revenue we expect to generate from product sales and under our existing collaborations, including milestones and royalties on Leqvio sales, should enable us to achieve a self-sustainable profile without the need for future equity financing, we will depend on our ability to generate product, collaboration and royalty revenues to achieve this goal. In addition to revenues derived from sales of our current and future, if any, commercially approved products, we anticipate that a portion of any revenues we generate over the next several years will continue to be from collaborations with pharmaceutical and biotechnology companies, including Roche, Regeneron, Sanofi and Novartis. We cannot be certain that we will be able to maintain our existing collaborations, secure and maintain new collaborations, meet our obligations under collaboration agreements, or achieve any milestones that we may be required to meet or achieve to receive payments under our existing or new collaborations. Moreover, we cannot be certain that our collaborators, including Novartis, will continue to successfully execute their obligations under our collaboration agreements and generate collaboration and royalty revenues for us.

To become and remain profitable, we must succeed in discovering, developing and commercializing novel product candidates with significant market potential. This will require us to build upon the success we have had in a range of challenging activities, including continued platform innovation, pre-clinical testing and clinical trial stages of development, obtaining regulatory approval and reimbursement for our novel product candidates and manufacturing, marketing and selling our approved products. We may never generate revenues that are significant enough to achieve profitability and, even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. If we cannot become and remain consistently profitable, the market price of our common stock could decline. In addition, we may be unable to raise capital, expand our business, develop additional product candidates or continue our operations.

We will require substantial funds to continue our research, development and commercialization activities, and if we require greater funds than we have estimated, we may need to critically limit, significantly scale back or cease certain activities.

We have used substantial funds to develop our RNAi technologies and will require substantial funds to conduct further research and development activities, including pre-clinical testing and clinical trials of our product candidates, and to manufacture, market and sell our four approved products and any other products that are approved for commercial sale.

Because the length of time or scope of activities associated with successful development of our product candidates may be greater than we anticipate, we are unable to estimate the actual funds needed to develop and commercialize our product candidates.

We believe 2019 was our peak operating loss year, and believe that our current cash, cash equivalents and marketable equity and debt securities, as well as revenue we expect to generate from product sales and under our current collaborations, including milestones and royalties we expect to receive from Novartis on Leqvio sales, will enable us to achieve a self-sustainable financial profile without the need for future equity financing. Nevertheless, our future capital requirements and the period for which our existing resources will support our operations may vary from what we currently expect. We have based our expectations on a number of factors, many of which are difficult to predict or are outside of our control, including:

- progress in our research and development programs, including programs in both rare and prevalent diseases, as well as what may be required by regulatory authorities to advance these programs;
- the timing, receipt and amount of milestone, royalty and other payments, if any, from present and future collaborators, if any, including milestone and royalty payments from Roche with respect to the development and commercialization of zilebesiran, as well as milestone and royalty payments from Novartis related to the commercialization of Leqvio;
- our ability to maintain and establish additional collaborations and/or new business initiatives;
- the potential for improved product profiles to emerge from our new technologies and our ability to successfully advance our delivery efforts in extrahepatic tissues;
- the resources, time and costs required to successfully initiate and complete our pre-clinical and clinical studies, obtain regulatory approvals, prepare for global commercialization of our product candidates and obtain and maintain licenses to third-party intellectual property;
- our ability to establish, maintain and operate our own manufacturing facilities in a timely and cost-effective manner;
- our ability to manufacture, or contract with third parties for the manufacture of, our product candidates for clinical testing and our products for commercial sale;
- the impact of any future pandemics or public health emergencies or the ongoing conflicts in the Middle East and Ukraine on the initiation or completion of pre-clinical studies or clinical trials and the supply of our products or product candidates;
- the resources, time and cost required for the preparation, filing, prosecution, maintenance and enforcement of patent claims;
- the costs associated with legal activities, including litigation and government investigations, arising in the course of our business activities and our ability to prevail or reach a satisfactory result in any such legal disputes and investigations;
- the timing, receipt and amount of sales milestones and royalties, if any, from our approved products and our potential products, if and when approved; and
- the outcome of the regulatory review process and commercial success of products for which we are entitled to receive royalties, including Leqvio.

If our estimates, predictions and financial guidance relating to these factors are incorrect, we may need to modify our operating plan and may be required to seek additional funding in the future. We may do so through either collaborative arrangements, public or private equity offerings or debt financings, royalty or other monetization transactions or a combination of one or more of these funding sources. Additional funds may not be available to us on acceptable terms or at all.

The terms of any financing we may be required to pursue in the future may adversely affect the holdings or the rights of our stockholders. If we raise additional funds by issuing equity securities, further dilution to our existing stockholders will result. In addition, as a condition to providing additional funding to us, future investors may demand, and may be granted, rights superior to those of existing stockholders.

If we require additional funding and are unable to obtain such funding on a timely basis, we may be required to significantly delay or curtail one or more of our research or development programs, or delay or curtail the further development of our global commercial infrastructure, and our ability to achieve our long-term strategic goals may be delayed or diminished. We also could be required to seek funds through arrangements with collaborators or others that may require us to relinquish rights to some of our technologies, product candidates or products that we would otherwise pursue on our own.

Although we sold a portion of the royalty stream and commercial milestones from the global sales of Leqvio by Novartis, we are entitled to retain the remaining portions of the future royalties and commercial milestone payments on Leqvio, and any negative developments related to Leqvio could have a material adverse effect on our receipt of those payments.

In April 2020, we sold to BX Bodyguard Royalties L.P. (an affiliate of The Blackstone Group Inc.), or Blackstone, 50% of the royalties payable to us with respect to net sales by Novartis, its affiliates or sublicensees of Leqvio and 75% of the commercial milestone payments payable to us under the MDCO agreement. If Blackstone does not receive royalty payments in respect of global sales of Leqvio equaling at least \$1.00 billion by December 31, 2029, Blackstone's interest in Leqvio royalties will increase to 55% (and our interest will decrease to 45%) effective January 1, 2030. As a result, any factor that has an adverse impact on sales of Leqvio could affect our ability to meet the \$1.00 billion repayment threshold in this timeframe, which in turn would have a negative impact on the percentage of the Leqvio royalty stream that we are entitled to retain.

Factors that could have an adverse impact on Leqvio sales include:

- companies working to develop new therapies or alternative formulations of products for HeFH and ASCVD;
- lack of acceptance of Leqvio by patients, the medical community or third party payors;
- any negative developments relating to Leqvio, such as safety, efficacy, or reimbursement issues;
- any disputes concerning patents or proprietary rights, or under license and collaboration agreements;
- foreign currency exchange rate fluctuations; and
- adverse regulatory or legislative developments that limit or prohibit the sale of Leqvio, such as restrictions on the use of Leqvio or safety-related label changes, including enhanced risk management programs.

If the revenues generated by sales of Leqvio are lower than expected, we may not receive commercial milestone payments and/or royalties in the amount we are currently anticipating, and our business, prospects, operating results and financial condition could be materially and adversely affected.

Geopolitical risks associated with the ongoing military conflict between Russia and Ukraine could have an adverse impact on our business, prospects, operating results and financial condition, including our clinical trials.

Russia's invasion of Ukraine, and the global response, including the imposition of sanctions by the U.S., EU and other countries, has resulted in global business disruptions and economic volatility and may have an adverse impact on our business, including our clinical trials. The uncertain nature, magnitude, and duration of hostilities stemming from the conflict in Ukraine, including the potential effects of sanctions retaliatory cyber-attacks on the world economy and markets, have contributed to increased market volatility and uncertainty, which could continue to have an adverse impact on macroeconomic factors that might affect our business and operations.

Additionally, the ongoing conflict in Ukraine has disrupted the ability of certain of our contract research organizations, or CROs, to conduct clinical trials at certain sites in Ukraine. We cannot be certain what the overall impact of this conflict will be on our ability to conduct and complete our clinical trials on schedule. However, interruptions of our clinical trials could significantly delay our clinical development plans and potential authorization or approval of our product candidates, which could increase our costs and jeopardize our ability to successfully commercialize our product candidates.

If the estimates we make, or the assumptions on which we rely, in preparing our financial statements and/or our projected guidance prove inaccurate, our actual results may vary from those reflected in our projections and accruals.

Our condensed consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America, or GAAP. The preparation of these condensed consolidated financial statements requires us to make estimates and judgments that affect the reported amounts of our assets, liabilities, revenues and expenses, the amounts of charges accrued by us and related disclosure of contingent assets and liabilities. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable under the circumstances. We cannot assure you, however, that our estimates, or the assumptions underlying them, will be correct.

Further, from time to time we issue financial guidance relating to our expectations regarding our combined product sales, collaboration and royalty revenues, and GAAP and non-GAAP combined research and development and selling, general and administrative expenses, which guidance is based on estimates and the judgment of our management. If, for any reason, our product sales, revenues and/or expenses differ materially from our guidance, we may have to adjust our publicly announced financial guidance. For example, in April 2022, we decreased our 2022 guidance range for combined net product revenues, and in October 2022, we decreased our guidance range for our collaboration and royalty revenue. If we fail to meet, or if we are required to change or update any element of, our publicly disclosed financial guidance or other expectations about our business, our stock price could decline.

The investment of our cash, cash equivalents and marketable securities is subject to risks which may cause losses and affect the liquidity of these investments.

As of March 31, 2024, we had \$2.37 billion in cash, cash equivalents and marketable securities. We historically have invested these amounts in high-grade corporate notes, commercial paper, securities issued or sponsored by the U.S. government, certificates of deposit and money market funds meeting the criteria of our investment policy, which is focused on the preservation of our capital. Corporate notes may also include foreign bonds denominated in U.S. dollars. These investments are subject to general credit, liquidity, market and interest rate risks. We may realize losses in the fair value of these investments or a complete loss of these investments, which would have a negative effect on our financial condition. In addition, should our investments cease paying or reduce the amount of interest paid to us, our interest income would decline. The market risks associated with our investment portfolio may have an adverse effect on our operating results, liquidity and financial condition.

Volatility in foreign currency exchange rates could have a material adverse effect on our operating results.

Our revenue from outside of the U.S. is expected to increase as our products, whether commercialized by us or our collaborators, gain marketing approval in such jurisdictions. Our primary foreign currency exposure relates to movements in the Japanese yen, Euro and British pound. If the U.S. dollar weakens against a specific foreign currency, our revenues will increase, having a positive impact on net income, but our overall expenses will increase, having a negative impact. Conversely, if the U.S. dollar strengthens against a specific foreign currency, our revenues will decrease, having a negative impact on net income, but our overall expenses will decrease, having a positive impact. For example, during 2022, the dollar strengthened against certain foreign currencies, and we experienced an unfavorable impact from foreign exchange rates on our international revenues. Continued volatility in foreign exchange rates is likely to continue to impact our operating results and financial condition.

Changes in tax laws could adversely affect our business, prospects, operating results and financial condition.

Our business is subject to numerous international, federal, state, and other governmental laws, rules, and regulations that may adversely affect our operating results, including, taxation and tax policy changes, tax rate changes, new tax laws, or revised tax law interpretations, which individually or in combination may cause our effective tax rate to increase. In the U.S., the rules dealing with federal, state, and local income taxation are constantly under review by persons involved in the legislative process and by the Internal Revenue Service and the U.S. Treasury Department. Changes to tax laws (which changes may have retroactive application) could adversely affect us or holders of our common stock. In recent years, many such changes have been made and changes are likely to continue to occur in the future. Future changes in tax laws could have a material adverse effect on our business, prospects, operating results and financial condition.

Additionally, the Organization for Economic Co-operation and Development, or the OECD, the EC, and individual taxing jurisdictions where we and our affiliates do business have recently focused on issues related to the taxation of multinational corporations. The OECD has released its comprehensive plan to create an agreed set of international rules for fighting base erosion and profit shifting. In addition, the OECD, the EC and individual countries are examining changes to how taxing rights should be allocated among countries considering the digital economy. As a result, tax laws in the U.S. and other countries in which we and our affiliates do business could change on a prospective or retroactive basis and any such changes could materially adversely affect our business, prospects, operating results and financial condition.

We may incur additional tax liabilities related to our operations.

We are subject to income tax in the U.S. and the foreign jurisdictions in which we operate. Significant judgment is required in determining our worldwide tax liabilities, and our effective tax rate is derived from the applicable statutory tax rates and relative earnings in each taxing jurisdiction. We record liabilities for uncertain tax positions that involve significant management judgment as to the application of law. Domestic or foreign taxing authorities may disagree with our interpretation of tax law as applied to our and our subsidiaries' operations or with the positions we may take with respect to particular tax issues on our tax returns. Consequently, tax assessments or judgments in excess of accrued amounts that we have estimated in preparing our financial statements may materially and adversely affect our reported effective tax rate or our cash flows. Further, other factors may adversely affect our effective tax rate, including changes in the mix of our profitability from country to country, tax effects of stock-based compensation (which depend in part on the price of our stock and, therefore, are beyond our control), and changes in tax laws or regulations. For example, the OECD Global Anti-Base Erosion Model have influenced tax laws in countries in which we operate, including the implementation of minimum taxes. Changes to these or other laws and regulations or their interpretations could materially and adversely impact our effective tax rate or cash flows.

Any future outbreaks of pandemics or public health emergencies, may directly or indirectly adversely affect our business, results of operations and financial condition.

In the future, we may experience disruptions from a pandemic or public health emergency that could impact our business and operations, including our ability to successfully commercialize our approved products, and we may not be able to meet expectations with respect to commercial sales as a result. In addition, we may also experience decreased patient demand for our approved products if current or potential patients decide to delay treatment as a result of a pandemic or public health

emergency. Business interruptions from pandemics or public health emergencies, including staffing shortages, raw material or other supply chain shortages, production slowdowns and disruptions in delivery systems, may also adversely impact the third parties we or our collaborators rely on in the U.S. and abroad to sufficiently manufacture our approved products and to produce product candidates in quantities we require, which may impair our commercialization efforts, our research and development activities and the potential commercialization of our product candidates.

Additionally, timely completion of pre-clinical activities and initiation of planned clinical trials are dependent upon the availability of, for example, pre-clinical and clinical trial sites, researchers and investigators, patients or healthy volunteer subjects available for recruitment and enrollment, and regulatory agency personnel, which may be adversely affected by global health matters, such as any pandemic or public health emergency. We are conducting and plan to continue to conduct pre-clinical activities and clinical trials for our drug product candidates in geographies which have been and may again be affected by COVID-19, and any resurgence of the COVID-19 pandemic and its variants, or the emergence of any future pandemic or public health emergency, could have an impact on various aspects of our ongoing clinical trials and on the clinical trials and pre-clinical studies we expect to initiate during 2024.

Health regulatory agencies globally may also experience disruptions in their operations as a result of a pandemic or future public health emergency, which could impact review, inspection and approval timelines. Since March 2020, when foreign and domestic inspections of facilities were largely placed on hold due to the COVID-19 pandemic, the FDA has been working to resume pre-pandemic levels of inspection activities, including routine surveillance, bioresearch monitoring and pre-approval inspections. Should the FDA determine that an inspection is necessary for approval of a marketing application and an inspection cannot be completed during the review cycle due to restrictions on travel, and the agency does not determine a remote interactive evaluation to be adequate, the FDA has stated that it generally intends to issue, depending on the circumstances, a complete response letter or defer action on the application until an inspection can be completed.

While the ultimate impact of any pandemic or public health emergency, on our business is uncertain, any negative impacts of such pandemic or public health emergency, alone or in combination with others, could exacerbate other risk factors discussed herein. The full extent to which any pandemic or public health emergency, will negatively affect our operations, financial performance, and stock price will depend on future developments that are highly uncertain and cannot be predicted.

Risks Related to Our Dependence on Third Parties

If we are unable to maintain our existing collaborations, or enter into new collaborations with other companies that can provide business and scientific capabilities and funds for the development and commercialization of our product candidates, it may have a negative impact on our business, prospects, operating results and financial condition.

We do not currently have adequate capacity or capabilities to advance all opportunities arising from our growing pipeline of RNAi therapeutics. Accordingly, we have entered into collaborations with third party collaborators we believe can provide such capacity and capabilities in certain territories and/or for certain product candidates, and we intend to enter into additional such collaborations in the future. Specifically, we currently have active collaborations with, among others, Roche, Regeneron, Sanofi, and Novartis covering various products and product candidates in our pipeline.

In such collaborations, we expect our current, and may expect our future, collaborators to provide substantial capabilities in clinical development, regulatory affairs, and/or marketing, sales and distribution. Under certain of our collaborations, we also expect our collaborators to develop, market and/or sell certain of our product candidates, in certain territories or globally, and we have limited or no control over the development, sales, marketing and distribution activities of these collaborators. Our future revenues may depend heavily on the success of the efforts of these third parties. For example, we will rely entirely on (i) Regeneron for the development and commercialization of all programs targeting eye diseases (subject to limited exceptions), and potentially other CNS and liver programs; (ii) Novartis for the development and commercialization of Leqvio worldwide; (iii) Sanofi for the development and commercialization of fitusiran worldwide; and (iv) Roche for the commercialization of zilebesiran outside of the U.S. In the case of each collaboration referenced in clauses (i)-(iv) above, we are entitled to royalties, and in some instances commercial milestone payments, on the sales of the applicable product. If our collaborators are not successful in their development and/or commercialization efforts, our future revenues from the relevant product or product candidate may be adversely affected. For example, in December 2020 Novartis received a complete response letter from the FDA stating that the FDA could not approve the NDA by the PDUFA action date due to unresolved inspection-related conditions at a third party manufacturing facility. While Leqvio was ultimately approved by the FDA in December 2021, the resolution of the complete response letter resulted in a delay in the payment of an approval milestone and potential U.S. royalties. As discussed above, under our agreement with Blackstone, if the revenues generated by the royalties received by Blackstone from us with respect to Leqvio sales do not reach a certain level by the end of 2029, Blackstone will be entitled to a higher royalty percentage beginning in 2030, which would have an adverse impact on our royalty revenues beginning in 2030.

We may not be successful in entering into future collaborations on terms favorable to us due to various factors, including our ability to demonstrate improved product profiles from our new technologies, including our IKARIA platform, our ability to successfully demonstrate proof-of-concept for our technology in humans in certain tissues or disease areas, our ability to demonstrate the safety and efficacy of our specific product candidates, our ability to manufacture or have third parties manufacture RNAi therapeutics, the strength of our intellectual property portfolio and/or concerns around challenges or

potential challenges to our intellectual property portfolio. Even when we succeed in securing such new collaborations, we may not be able to maintain them if, for example, development or approval of a product candidate is delayed, challenges are raised as to the validity or scope of our intellectual property, we are unable to secure adequate reimbursement from payors, sales of an approved drug are lower than we expected, or our collaborator changes its strategic focus.

Furthermore, any delay in entering into new collaboration agreements would have the potential to prevent or delay the development and commercialization of certain product candidates, or reduce the competitiveness such product candidates if they ultimately reach the market, which in turn could adversely affect our business, prospects, operating results and financial condition.

For certain product candidates, we have formed collaborations to fund all or part of the costs of drug development and commercialization, such as our collaborations with Roche, Regeneron, Sanofi and Novartis. We may not, however, be able to enter into additional collaborations for certain other programs, and the terms of any collaboration agreements we do secure may not be favorable to us. If we are not successful in our efforts to enter into future collaboration arrangements with respect to one or more of our product candidates, we may not have sufficient funds or other resources to develop these product candidates or other product candidates internally, or to bring such product candidates to market. In these circumstances, we will not be able to generate revenues from these product candidates, and this will substantially harm our business, prospects, operating results and financial condition.

If any collaborator materially amends, terminates or fails to perform its obligations under agreements with us, the development and commercialization of our product candidates could be delayed or terminated.

Our dependence on collaborators for capabilities and funding means that our business could be adversely affected if any collaborator materially amends or terminates its collaboration agreement with us or fails to perform its obligations under that agreement. Our current or future collaborations, if any, may not be scientifically or commercially successful. Disputes may arise in the future with respect to the ownership of rights to technology or products developed with collaborators, which could have an adverse effect on our ability to develop and commercialize any affected product candidate. Our current collaborations allow, and we expect that any future collaborations will allow, either party to terminate the collaboration for a material breach by the other party. In addition, our collaborators may have additional termination rights for convenience with respect to the collaboration or a particular program under the collaboration, under certain circumstances. For example, our agreement with Novartis relating to the development and commercialization of inclisiran worldwide may be terminated by Novartis at any time upon four months' prior written notice, provided if the agreement is terminated by Novartis for convenience, Novartis must grant a license to us under certain technology developed in the course of its (or MDCO's) activities under the agreement, subject to a royalty to be negotiated between the parties. Moreover, any adverse actions by Novartis with respect to the MDCO License Agreement or disputes with Novartis regarding the MDCO License Agreement could adversely impact our ability to comply with our obligations under our agreements with Blackstone. If we were to lose a commercialization collaborator, we would have to attract a new collaborator (potentially on less favorable terms for us than we have with our existing collaborator) or develop expanded sales, distribution and marketing capabilities internally, which would require us to invest significant amounts of financial and management resources.

In addition, if we have a dispute with a collaborator over the ownership of technology or other matters, or if a collaborator terminates its collaboration with us, for breach or otherwise, or determines not to pursue the research, development and/or commercialization of the affected product or product candidate, it could delay our development of product candidates, result in the need for additional company resources to develop product candidates, require us to expend time and resources to develop expanded sales and marketing capabilities on a more expedited timeline, make it more difficult for us to attract new collaborators and could adversely affect how we are perceived in the business and financial communities.

Moreover, a collaborator, or in the event of a change in control of a collaborator or the assignment of a collaboration agreement to a third party, the successor entity or assignee, as in the case of MDCO and Novartis, could determine that it is in its interests to:

- pursue alternative technologies or develop alternative products, either on its own or jointly with others, that may be competitive with the products on which it is collaborating with us or which could affect its commitment to the collaboration with us;
- pursue higher-priority programs or change the focus of its development programs, which could affect the collaborator's commitment to us; or
- if it has marketing rights, choose to devote fewer resources to the marketing of our product candidates, if any are approved for marketing, than it does for product candidates developed without us.

If any of these occur, the development and commercialization of one or more products or product candidates could be delayed, curtailed or terminated because we may not have sufficient financial resources or capabilities to continue such development and commercialization on our own.

We expect to continue to grow our manufacturing capabilities and resources and we must incur significant costs to develop this expertise and/or rely on third parties to manufacture our products.

We have been expanding our manufacturing capabilities, and to continue to commercialize our approved products, continue to develop our current product candidates, apply for regulatory approvals and, if approved, commercialize future products, we will need to continue to develop our internal manufacturing capabilities and/or contract or otherwise arrange for any necessary external manufacturing capabilities. Historically, our internal manufacturing capabilities were limited to small-scale production of material for use in in vitro and in vivo experiments and such material was not required to be produced under current good manufacturing practice standards, or cGMP. During 2012, we developed cGMP capabilities and processes for the manufacture of patisiran formulated bulk drug product for late-stage clinical trial use and commercial supply. In addition, during 2020, we completed construction and qualification of our cGMP manufacturing facility in Norton, Massachusetts where we manufacture drug substances for early-stage clinical development and have the possibility to manufacture drug substances for late-stage clinical development and commercial use, in the future.

At the present time, we only have the capacity to manufacture limited quantities of clinical trial drug substance ourselves, and otherwise we continue to rely on third party CMOs to manufacture additional drug substance, and we rely on third party CMOs for all of our drug product requirements for clinical and commercial use. There are a limited number of CMOs worldwide with the expertise to manufacture our siRNA therapeutic products, and we currently rely on a limited number of CMOs in North America, Europe and Asia to manufacture our products and product candidates. There are risks inherent in pharmaceutical manufacturing that could affect the ability of our CMOs to meet our delivery time requirements or provide adequate amounts of material to meet our needs, and if our CMOs fail to do these things it could delay our clinical trials and potentially put our commercial supply at risk, as well as result in additional expense to us. To fulfill our future requirements, we will likely need to contract with additional CMOs, and such alternative suppliers may be limited, not be readily available, or we may be unable to enter into agreements with them on reasonable terms and in a timely manner, or at all.

In addition to the manufacture of synthetic siRNAs, we may have additional manufacturing requirements related to the technology required to deliver the siRNA to the relevant cell or tissue type, such as LNPs or conjugates or other drug delivery technologies. In some cases, the delivery technology we utilize is highly specialized or proprietary, and for technical and/or legal reasons, we may have access to only one or a limited number of potential manufacturers for such delivery technology. In addition, the scale-up of our delivery technologies could be very difficult and/or take significant time. We also have limited experience in such scale-up and manufacturing, requiring us to depend on a limited number of third parties, who might not be able to deliver in a timely manner, or at all. Failure by manufacturers to properly manufacture our delivery technology and/or formulate our siRNAs for delivery could result in unusable product, supply delays and drug shortages. Furthermore, competition for supply from our manufacturers from other companies, a breach by such manufacturers of their contractual obligations or a dispute with such manufacturers would cause delays in our discovery and development efforts, as well as additional expense to us.

In developing manufacturing capabilities by building our own manufacturing facilities, we have incurred substantial expenditures, and expect to incur significant additional expenditures in the future. Also, we have had to, and will likely need to continue to, recruit, hire, and train qualified employees to staff our facilities. If we are unable to manufacture sufficient quantities of material or if we encounter problems with our facilities in the future, we may also need to secure alternative suppliers, and such alternative suppliers may not be available, or we may be unable to enter into agreements with them on reasonable terms and in a timely manner, or at all. Given our dependence on a limited number of CMOs to supply our commercial products and clinical candidates, and the ongoing utilization of our own facilities, any delay or setback in the manufacture of our products could impede ongoing clinical and commercial supply, which could materially and adversely impact our business, prospects, operating results or financial condition. In addition, to the extent we or our collaborators rely on CMOs to supply our product candidates, any delays or disruptions in supply could have a material adverse impact on the research and development activities and potential commercialization of our or our collaborators' product candidates.

The manufacturing processes for our products and any other product candidates that we may develop is subject to the FDA and foreign regulatory authority approval process and we will need to meet, and will need to contract with CMOs who can meet, all applicable FDA and foreign regulatory authority requirements on an ongoing basis. The failure of any CMO to meet required regulatory authority requirements could result in the delayed submission of regulatory applications, or delays in receiving regulatory approval for any of our or our current or future collaborators' product candidates. For example, in April 2022, due to an amendment to our vutrisiran NDA submission to address a pending inspection classification at a third-party secondary packaging and labeling facility, the FDA extended the review timeline of the NDA. In addition, if we receive the necessary regulatory approval for any product candidate, we also expect to rely on third parties, including potentially our commercial collaborators, to produce materials required for commercial supply.

Additionally, in January 2024, there was congressional activity, including the introduction of the BIOSECURE ACT (H.R. 7085) in the House of Representatives and a substantially similar bill (S.3558) in the Senate. If these bills became law, or similar laws are passed, they would have the potential to severely restrict the ability of U.S. biopharmaceutical companies like us to purchase services or products from, or otherwise collaborate with, certain Chinese "biotechnology companies of concern" without losing the ability to contract with, or otherwise receive reimbursement from, the U.S. government. We do business with

companies in China and it is possible some of our contractual counterparties could be impacted by the legislation described above.

If the third parties we engage to supply materials or manufacture product candidates or products for preclinical testing or clinical or commercial supply should cease to do so for any reason, we would likely experience delays in advancing these preclinical tests and clinical trials and/or interruptions in commercial supply while we identify and qualify replacement suppliers or manufacturers, and we may be unable to obtain replacement supplies on terms that are favorable to us, or at all. If we are not able to obtain adequate supplies of our product candidates or products or the substances used to manufacture them, it could materially and adversely impact our business, prospects, operating results or financial condition.

To the extent that we have existing, or enter into future, manufacturing arrangements with third parties, we depend, and will depend in the future, on these third parties to perform their obligations in a timely manner and consistent with contractual and regulatory requirements, including those related to quality control and quality assurance. The failure of any CMO to perform its obligations as expected, or, to the extent we manufacture all or a portion of our product candidates ourselves, our failure to execute on our manufacturing requirements, could adversely affect our business in a number of ways, including:

- we or our current or future collaborators may not be able to initiate or continue clinical trials of product candidates that are under development;
- we or our current or future collaborators may be delayed in submitting regulatory applications, or receiving regulatory approvals, for our product candidates;
- we may lose the cooperation of our collaborators;
- our facilities and those of our CMOs, and our products could be the subject of inspections by regulatory authorities that could have a negative outcome and result in supply delays;
- we may be required to cease distribution or recall some or all batches, of our products or take action to recover clinical trial material from clinical trial sites; and
- ultimately, we may not be able to meet the clinical and commercial demands for our product candidates and products.

We rely on third parties to conduct our clinical trials, and if such third parties fail to fulfill their obligations, our development plans may be adversely affected.

We rely on independent clinical investigators, CROs, and other third-party service providers to assist us in managing, monitoring and otherwise carrying out our clinical trials. We have contracted with, and we plan to continue to contract with, certain third parties to provide certain services, including site selection, enrollment, monitoring, auditing and data management services. These investigators and CROs are not our employees and we have limited control over the amount of time and resources they dedicate to our programs. These third parties may have contractual relationships with other entities, some of which may be our competitors, which may draw their time and resources away from our programs. Although we depend heavily on these parties, we control only limited aspects of their activity and therefore, we cannot be assured that these third parties will adequately perform all of their contractual obligations to us in compliance with regulatory and other legal requirements and our internal policies and procedures. 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 third parties does not relieve us of our regulatory responsibilities. We and our CROs are required to comply with applicable good clinical practice, or GCP, requirements, which are regulations and guidelines enforced by the FDA and comparable foreign regulatory authorities for our product candidates in clinical development, and to implement timely corrective action to address any non-compliance. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, principal investigators and trial sites, including in connection with the review of marketing applications. If we or any of our CROs fail to comply with applicable GCP requirements, or fail to take any such corrective action, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, EMA, PMDA or other foreign regulatory authorities may require us to take additional action or perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority in the future, such regulatory authority will determine that any of our clinical trials comply with GCP regulations.

If our third-party service providers cannot adequately and timely fulfill their obligations to us for any reason, or if the quality and accuracy of our clinical trial data is compromised due to failure by such third party service provider to adhere to our protocols or regulatory requirements or if such third party service providers otherwise fail to meet deadlines, our development plans and/or regulatory reviews for marketing approvals may be delayed or terminated. As a result, our business, prospects, operating results and financial condition would be harmed, and our stock price would likely be negatively impacted.

Before conducting clinical trials to demonstrate the safety and efficacy of our product candidates in humans in support of IND applications or similar applications in other jurisdictions, we must complete pre-clinical studies, which includes animal studies. In addition, we rely on third-party service providers to source certain materials for such pre-clinical studies. Our ability to complete our pre-clinical studies is contingent on, among other things, our ability to source animals and other supplies required for the conduct of such studies. If we are unable to obtain such supplies, we may be unable to complete such pre-

clinical studies in a timely manner or at all. For example, some of our IND-enabling toxicology and other studies require certain non-human primates that have customarily been imported from the People's Republic of China and Cambodia, and the supply of these non-human primates was constrained in 2022 due to various factors. If we were to encounter delays in obtaining a sufficient supply of such non-human primates to enable the conduct of our pre-clinical studies, our ability to complete pre-clinical studies could be impaired and our submission of IND applications and similar applications in other jurisdictions could be delayed, which would have an adverse impact on the development timelines of the impacted product candidates.

Risks Related to Managing Our Operations

If we are unable to attract and retain qualified key management and scientists, development, medical and commercial staff, consultants and advisors, our ability to implement our business plan may be adversely affected.

We are highly dependent upon our senior management and our scientific, clinical, sales and medical staff. The loss of the service of any members of our senior management could significantly delay or prevent the achievement of product development and commercialization, and other business objectives, and adversely impact our stock price. Our employment arrangements with our key personnel are terminable without notice. We do not carry key person life insurance on any of our employees.

We have grown our workforce significantly over the past several years and anticipate additional employee growth in the future, and we face intense competition for qualified individuals from numerous pharmaceutical and biotechnology companies, universities, governmental entities and other research institutions, many of which have substantially greater resources to attract and reward qualified individuals than we do. In addition, if we are not successful in commercializing our approved products, we may be unable to attract and retain highly qualified sales and marketing professionals, and if we are not able to attract and retain qualified sales and marketing professionals, it would negatively impact our ability to commercialize our approved products and any future products. Accordingly, we may be unable to attract and retain suitably qualified individuals to support our growing research, development and global commercialization efforts and initiatives, and our failure to do so could have an adverse effect on our ability to implement our future business plans.

We may have difficulty expanding our operations successfully as we continue our evolution from a U.S.- and EU-based company primarily involved in discovery, pre-clinical testing and clinical development into a global company that develops and commercializes multiple products.

As we continue the commercial launches of our approved products, and increase the number of product candidates we are developing, we will need to continue to expand our operations in the U.S. and further develop operations in the EU and other geographies, including Asia and Latin America. To date, we have received regulatory approval for four products, which we have launched in multiple geographies globally, and we continue to expand the reach of these products with additional regulatory filings and launches.

We have grown our workforce significantly over the last several years and anticipate additional employee growth globally in the future as we focus on the commercialization of our approved products, and achieving our *Alynlam P⁵x25* strategy. This growth has placed a strain on our administrative and operational infrastructure and, as a result, we will need to continue to develop additional and/or new infrastructure and capabilities to support our growth and obtain additional space to conduct our global operations in the U.S., EU, Japan, Latin America and other geographies. If we are unable to develop such additional infrastructure or obtain sufficient space to accommodate our growth in a timely manner and on commercially reasonable terms, our business could be negatively impacted. As we continue the commercialization of our approved products, and as the product candidates we develop enter and advance through clinical trials, we will need to continue to expand our global development, regulatory, manufacturing, quality, compliance, and marketing and sales capabilities, or contract with other organizations to provide these capabilities for us. In addition, as our operations continue to expand, we will need to successfully manage additional relationships with various collaborators, suppliers, distributors and other organizations. Our ability to manage our operations and future growth will require us to continue to enhance our operational, financial and management controls and systems, reporting systems and infrastructure, ethics and compliance functions, and policies and procedures. We may not be able to implement enhancements to our management information and control systems in an efficient or timely manner and may discover deficiencies in existing systems and controls.

The use of social media presents risks and challenges.

Social media is being used to communicate about our clinical development programs and the diseases our investigational RNAi therapeutics are being developed to treat, and we are utilizing what we believe is appropriate social media in connection with our commercialization efforts for our approved products, and we intend to do the same for our future products, if approved. Social media practices in the biopharmaceutical industry continue to evolve and regulations and regulatory guidance relating to such use are evolving and not always clear. This evolution creates uncertainty and risk of noncompliance with regulations applicable to our business, resulting in potential regulatory actions against us, along with the potential for litigation related to off-label marketing or other prohibited activities. For example, for our clinical-stage candidates, patients may use social media channels to comment on their experience in an ongoing blinded clinical study or to report an alleged adverse event, or AE. When such disclosures occur, there is a risk that study enrollment may be adversely impacted, we fail to monitor and comply with applicable AE reporting obligations or that we may not be able to defend our business in the face of the political

and market pressures generated by social media due to restrictions on what we may say about our investigational products. There is also a risk of inappropriate disclosure of sensitive information or negative or inaccurate posts or comments about us on any online platform, including a blog on the internet, or a post on a website, that can be distributed rapidly and could negatively harm our reputation. If any of these events were to occur or we otherwise fail to comply with applicable regulations, we could incur liability, face regulatory actions or incur other harm to our business.

Our business and operations could suffer in the event of system failures or unauthorized or inappropriate use of or access to our systems.

We are increasingly dependent on our information technology systems and infrastructure for our business. We collect, store and transmit sensitive information including intellectual property, proprietary business information, including highly sensitive clinical trial data, and personal information in connection with our business operations. The secure maintenance of this information is critical to our operations and business strategy. Some of this information could be subject to criminal attack or unauthorized access and use by third parties with a wide range of motives and expertise, including organized criminal groups, “hacktivists,” patient groups, disgruntled current or former employees and others. Cyber-attacks are of ever-increasing levels of sophistication, and despite our security measures, our information technology and infrastructure may be vulnerable to such attacks or may be breached, including due to employee error or malfeasance.

The pervasiveness of cybersecurity incidents in general and the risks of cyber-crime are complex and continue to evolve. Although we are making significant efforts to maintain the security and integrity of our information systems and are exploring various measures to manage the risk of a security breach or disruption, there can be no assurance that our security efforts and measures will be effective or that attempted security breaches or disruptions would not be successful or damaging. Despite the implementation of security measures, our internal computer systems and those of our contractors, consultants and collaborators are vulnerable to damage or interruption from computer viruses, unauthorized or inappropriate access or use, natural disasters, pandemics or public health emergencies, terrorism, war (including the ongoing conflicts in Ukraine and the Middle East), and telecommunication and electrical failures. Such events could cause interruption of our operations. For example, the loss of pre-clinical trial data or data from completed or ongoing clinical trials for our product candidates could result in delays in our regulatory filings and development efforts, as well as delays in the commercialization of our products, and significantly increase our costs. To the extent that any disruption, security breach or unauthorized or inappropriate use or access to our systems were to result in a loss of or damage to our data, or inappropriate disclosure of confidential or proprietary information, including but not limited to patient, employee or vendor information, we could incur notification obligations to affected individuals and government agencies, liability, including potential lawsuits from patients, collaborators, employees, stockholders or other third parties, and liability under foreign, federal and state laws that protect the privacy and security of personal information, and the development and potential commercialization of our product candidates could be delayed.

In addition, our increased use of cloud technologies heightens these third party and other operational risks, and any failure by cloud or other technology service providers to adequately safeguard their systems and prevent cyber-attacks could disrupt our operations and result in misappropriation, corruption, or loss of confidential or propriety information. The risk of cyber-attacks is increased with employees working remotely. Remote work increases the risk we may be vulnerable to cybersecurity-related events such as phishing attacks and other security threats.

Risks Related to Our Industry

Risks Related to Development, Clinical Testing and Regulatory Approval of Our Product Candidates and the Commercialization of Our Approved Products

Any product candidate we or our collaborators develop may fail in development or be delayed to a point where such product candidate does not become commercially viable.

Before obtaining regulatory approval for the commercial distribution of our product candidates, we must conduct, at our own expense, extensive nonclinical tests and clinical trials to demonstrate the safety and/or efficacy in humans of our product candidates. Nonclinical and clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome, and the historical failure rate for product candidates is high. We currently have multiple programs in clinical development, including internal and collaborated programs in Phase 3 development, as well as several earlier-stage clinical programs. However, we may not be able to further advance any of our product candidates through clinical trials and regulatory approval.

If we enter into clinical trials, the results from nonclinical testing or early or late stage clinical trials of a product candidate may not predict the results that will be obtained in subsequent subjects or in subsequent human clinical trials of that product candidate or any other product candidate. For example, we are conducting the HELIOS-B Phase 3 clinical trial of vutrisiran, which is investigating the potential of vutrisiran to treat the cardiac manifestations of disease in patients with ATTR amyloidosis with cardiomyopathy. While vutrisiran has demonstrated positive results in patients with hATTR amyloidosis with polyneuropathy, we cannot be certain that the results from HELIOS-B will be positive or that the results from HELIOS-B will support approval of vutrisiran for the treatment of patients with ATTR amyloidosis with cardiomyopathy. There is a high failure rate for drugs proceeding through clinical studies. A number of companies in the pharmaceutical and biotechnology

industries have suffered significant setbacks in clinical development even after achieving promising results in earlier studies, and any such setbacks in our clinical development, including with respect to vutrisiran, could have a material adverse effect on our business, prospects, operating results and financial condition. Moreover, our approved products and our current product candidates, employ novel delivery technologies that, with the exception of inclisiran, have yet to be extensively evaluated in human clinical trials and proven safe and effective.

Additionally, several of our planned and ongoing clinical trials utilize an “open-label” trial design. An “open-label” clinical trial is one where both the patient and investigator know whether the patient is receiving the investigational product candidate or either an existing approved drug or placebo. Most typically, open-label clinical trials test only the investigational product candidate and sometimes may do so at different dose levels. Open-label clinical trials are subject to various limitations that may exaggerate any therapeutic effect as patients in open-label clinical trials are aware when they are receiving treatment. Accordingly, open-label clinical trials may be subject to a “patient bias” where patients perceive their symptoms to have improved merely due to their awareness of receiving an experimental treatment. In addition, open-label clinical trials may be subject to an “investigator bias” where those assessing and reviewing the physiological outcomes of the clinical trials are aware of which patients have received treatment and may interpret the information of the treated group more favorably given this knowledge. The results from an open-label trial may not be predictive of future clinical trial results with any of our product candidates when studied in a blinded, controlled environment with a placebo or active control.

In addition, we, the FDA or other applicable regulatory authorities, or an institutional review board, or IRB, or similar foreign review board or committee, may delay initiation of or suspend clinical trials of a product candidate at any time for various reasons, including if we or they believe the healthy volunteer subjects or patients participating in such trials are being exposed to unacceptable health risks. Among other reasons, adverse side effects of a product candidate or related product on healthy volunteer subjects or patients in a clinical trial could result in our decision, or a decision by the FDA or foreign regulatory authority, to suspend or terminate the clinical trial, or, in the case of regulatory agencies, a refusal to approve a particular product candidate for any or all indications of use.

Clinical trials of a new product candidate require the enrollment of a sufficient number of patients, including patients who are suffering from the disease the product candidate is intended to treat and who meet other eligibility criteria. Rates of patient enrollment are affected by many factors, including the size of the patient population, the age and condition of the patients, the stage and severity of disease, the availability of clinical trials for other investigational drugs for the same disease or condition, the nature of the protocol, the proximity of patients to clinical sites, the availability of effective treatments for the relevant disease, and the eligibility criteria for the clinical trial. We or our collaborators may experience difficulty enrolling our clinical trials due to the availability of existing approved treatments, as well as other investigational treatments in development. For example, in November 2018 we announced that due to recruitment challenges, we had discontinued a Phase 2 study of cemdisiran in atypical hemolytic uremic syndrome and were focusing our cemdisiran clinical development efforts in a different indication. Delays or difficulties in patient enrollment, or difficulties retaining trial participants, including as a result of the availability of existing approved treatments or other investigational treatments or safety concerns, including the impact of pandemics or other public health emergencies, can result in increased costs, longer development times or termination of a clinical trial.

Although our RNAi therapeutics have been generally well-tolerated in our clinical trials to date, new safety findings may emerge. The occurrence of serious adverse events, or SAEs, and/or adverse events, or AEs, can result in the suspension or termination of clinical trials of a product candidate by us, our collaborators, or the FDA or a foreign regulatory authority, and may negatively impact the clinical and/or regulatory timelines of the impacted product candidates. For example, in October 2016, we discontinued our revusiran program and in September 2017, we announced that we had temporarily suspended dosing in all ongoing fitusiran studies pending further review of a fatal thrombotic SAE that occurred in a patient who was receiving fitusiran in our Phase 2 OLE study. More recently, in October 2020, Sanofi voluntarily paused dosing in all ongoing fitusiran clinical studies to assess reports of non-fatal thrombotic events in patients participating in the ATLAS Phase 3 program. Following an assessment of available data and alignment with regulators, patients restarted on fitusiran under amended protocols in ongoing clinical studies and, in October 2021, Sanofi announced that a potential filing date for fitusiran had been moved to 2024 due to the introduction of a revised dosing regimen in the ongoing phase 3 studies. In addition, the occurrence of SAEs and/or AEs could also result in refusal by the FDA or a foreign regulatory authority to approve a particular product candidate for any or all indications of use, or in limitations in the label of any approved product.

In addition, the occurrence of SAEs and/or AEs could also result in refusal by the FDA or a foreign regulatory authority to approve a particular product candidate for any or all indications of use, or in limitations in the label of any approved product.

Clinical trials also require the review, oversight and approval of IRBs, or, outside of the U.S., independent ethics committees, which continually review clinical investigations and protect the rights and welfare of human subjects. Inability to obtain or delay in obtaining IRB or ethics committee approval can prevent or delay the initiation and completion of clinical trials, and the FDA or foreign regulatory authorities may decide not to consider any data or information derived from a clinical trial not subject to initial and continuing IRB or ethics committee review and approval, as the case may be, in support of a marketing application.

Our product candidates that may encounter problems during clinical trials that will cause us, an IRB, ethics committee or regulatory authorities to delay, suspend or terminate these clinical trials, or that will delay or confound the analysis of data from these clinical trials. If our product candidates experience any such problems, we may not have the financial resources necessary to continue development of the affected product candidate or any of our other product candidates. We may also lose, or be unable to enter into, collaborative arrangements for the affected product candidate or any of our other product candidates.

A failure of one or more of our clinical trials can occur at any stage of testing. We may experience numerous unforeseen events during, or as a result of, nonclinical testing and the clinical trial process that could extend our clinical development timelines and delay or prevent regulatory approval or our ability to commercialize our product candidates, including:

- our nonclinical tests or clinical trials may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional nonclinical testing or clinical trials, or we may abandon projects that have the potential to be promising;
- delays in filing IND applications or comparable foreign applications or delays or failure in obtaining the necessary approvals from regulators or IRBs/ethics committees in order to commence a clinical trial at a prospective trial site, or their suspension or termination of a clinical trial once commenced;
- conditions imposed on us by an IRB or ethics committee, or the FDA or comparable foreign regulatory authorities regarding the scope or design of our clinical trials;
- problems in engaging IRBs or ethics committees to oversee clinical trials or problems in obtaining or maintaining IRB or ethics committee approval of clinical trials;
- delays in enrolling patients and volunteers into clinical trials, and variability in the number and types of patients and volunteers available for clinical trials, including as a result of the COVID-19 pandemic, a future pandemic or public health emergency and the ongoing conflict in Ukraine;
- disruptions caused by man-made or natural disasters or pandemics, epidemics or public health emergencies or other business interruptions;
- high drop-out rates for patients and volunteers in clinical trials;
- negative or inconclusive results from our clinical trials or the clinical trials of others for product candidates similar to ours;
- inadequate supply or quality of product candidate materials or other materials necessary for the conduct of our clinical trials or disruption or delays in clinical supply due to the COVID-19 or a future pandemic or public health emergency;
- greater than anticipated clinical trial costs;
- serious and unexpected drug-related side effects experienced by patients taking our approved products, participants in our clinical trials or individuals using drugs similar to our products or product candidates;
- poor or disappointing effectiveness of our product candidates during clinical trials;
- unfavorable FDA or other regulatory agency inspection and review of a clinical trial site or records of any clinical or nonclinical investigation;
- failure of our third-party contractors or investigators to comply with regulatory requirements, including GCP and cGMP, or otherwise meet their contractual obligations in a timely manner, or at all;
- governmental or regulatory delays and changes in regulatory requirements, policy and guidelines, including the imposition of additional regulatory oversight around clinical testing generally or with respect to our technology in particular; or
- interpretations of data by the FDA and similar foreign regulatory agencies that differ from ours.

Even if we successfully complete clinical trials of our product candidates, any given product candidate may not prove to be a safe and effective treatment for the disease for which it was being tested.

We or our collaborators may be unable to obtain U.S. or foreign regulatory approval for our or our collaborated product candidates and, as a result, we or our collaborators may be unable to commercialize such product candidates.

Our and our collaborated product candidates are subject to extensive governmental regulations relating to, among other things, research, testing, development, manufacturing, safety, efficacy, approval, recordkeeping, reporting, labeling, storage, pricing, marketing and distribution of drugs. Rigorous nonclinical testing and clinical trials and an extensive regulatory approval process are required to be successfully completed in the U.S. and in many foreign jurisdictions before a new drug can be marketed. Satisfaction of these and other regulatory requirements is costly, time consuming, uncertain and subject to unanticipated delays. It is possible that the product candidates we and our collaborators are developing will not obtain the regulatory approvals necessary for us or our collaborators to begin selling them, or, in the case of vutrisiran, will not obtain

regulatory approval to be sold for an additional, broader indication than the indication for which it is currently approved. It is also possible that the FDA or other regulatory authorities may determine that the data generated in clinical trials for a product candidate is not sufficient to support the approval of an application for regulatory approval. For example, although we reported positive results from the APOLLO-B Phase 3 study of patisiran in patients with ATTR amyloidosis with cardiomyopathy, and received a 9:3 vote from the FDA's CRDAC that patisiran's benefits outweighed its risks for the treatment of ATTR amyloidosis with cardiomyopathy, in October 2023, the FDA issued a CRL in response to our sNDA for patisiran, indicating the sNDA could not be approved in its present form.

The time required to obtain FDA and other regulatory approvals is unpredictable but typically takes many years following the commencement of clinical trials, depending upon the type, complexity and novelty of the product candidate. The standards that the FDA and its foreign counterparts use when regulating us are not always applied in a predictable or uniform manner and can change over time. Any analysis we perform of data from nonclinical and clinical activities is subject to confirmation and interpretation by regulatory authorities, which could delay, limit or prevent regulatory approval. We or our collaborators may also encounter unexpected delays or increased costs due to new government regulations, for example, from future legislation or administrative action, or from changes in FDA policy during the period of product development, clinical trials and FDA regulatory review. It is impossible to predict whether legislative changes will be enacted, or whether FDA or foreign regulations, guidance or interpretations will be changed, or what the impact of such changes, if any, may be.

Because the product candidates we or our collaborators are developing represent a new class of drug, the FDA and its foreign counterparts have not yet established any definitive policies, practices or guidelines in relation to these drugs. The lack of policies, practices or guidelines may hinder or slow review by the FDA of any regulatory filings that we or our collaborators may submit. Moreover, the FDA may respond to these submissions by defining requirements we or our collaborators may not have anticipated. Such responses could lead to significant delays and increased costs in the development of our or our collaborated product candidates. In addition, because there may be approved treatments for some of the diseases for which we or our collaborators may seek approval, including vutrisiran for the treatment of ATTR amyloidosis with cardiomyopathy, or treatments in development which are approved by the time we or our collaborators file for approval, in order to receive regulatory approval, we or they may need to demonstrate through clinical trials that the product candidates we develop to treat these diseases are not only safe and effective, but safer and/or more effective than existing approved products. Interruption or delays in the operations of the FDA, EMA and comparable foreign regulatory agencies may impact the review, inspection and approval timelines for our or our collaborated product candidates. During the COVID-19 public health emergency, the FDA worked to ensure timely reviews of applications for medical products in line with its user fee performance goals and conducted mission critical domestic and foreign inspections to ensure compliance of manufacturing facilities with FDA quality standards. In addition, during the COVID-19 public health emergency, a number of companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. In December 2020, the FDA issued a CRL regarding Novartis' NDA for inclisiran, stating that the agency could not approve the NDA by the PDUFA action date due to unresolved facility inspection-related conditions. In July 2021, Novartis announced that the resubmission to the FDA of the inclisiran NDA to address the complete response letter was filed, and the FDA approved Leqvio (the trade name under which inclisiran is marketed in the U.S.) in December 2021. This delay in the approval of Leqvio resulted in delayed milestone and royalty revenue to us. Any similar interruption or delay by the FDA, EMA or comparable foreign regulatory authorities could have a material adverse effect on our or our collaborators' efforts to obtain regulatory approval for our or our collaborators' product candidates, which could have a material adverse effect on our business, prospects, operating results or financial condition. For instance, the FDA may request additional clinical or other data or information in connection with the regulatory review of our or our collaborators' product candidates, including by issuing a complete response letter that may require that we or our collaborators submit additional clinical or other data or impose other conditions that must be met in order to secure final approval of our or our collaborators' NDA applications, including potentially requiring a facility inspection. Even if such data and information are submitted, or any such inspection is completed, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval.

Any delay or failure in obtaining required approvals for our product candidates or our collaborated product candidates could have a material adverse effect on our ability to generate revenues from any product candidate for which we or our collaborators may seek approval in the future. For example, as a result of the recent CRL from the FDA in response to our sNDA for patisiran as a treatment for ATTR amyloidosis with cardiomyopathy, our ability to generate product revenues for patisiran will be negatively impacted. Furthermore, any regulatory approval to market any product may be subject to limitations on the approved uses for which we or our collaborators may market the product or the labeling or other restrictions, which could limit each such product's market opportunity and have a negative impact on our business, prospects, operating results and financial condition and our stock price. In addition, the FDA has the authority to require a Risk Evaluation and Mitigation Strategy, or REMS, plan as part of its review of an NDA, or after approval, which may impose further requirements or restrictions on the distribution or use of an approved drug, such as limiting prescribing to certain physicians or medical centers that have undergone specialized training, limiting treatment to patients who meet certain safe-use criteria and requiring treated patients to enroll in a registry. In the EU, we or our collaborators could be required to adopt a similar plan, known as a risk management plan, and our products could be subject to specific risk minimization measures, such as restrictions on prescription and supply, the conduct of post-marketing safety or efficacy studies, or the distribution of patient and/or prescriber educational

materials. In either instance, these limitations and restrictions may limit the size of the market for our products and affect reimbursement by third-party payors.

We are also subject to numerous foreign regulatory requirements governing, among other things, the conduct of clinical trials, manufacturing and marketing authorization, pricing and third-party reimbursement. The foreign regulatory approval process varies among countries and includes all of the risks associated with FDA approval described above as well as risks attributable to the satisfaction of local regulations in foreign jurisdictions. Approval by the FDA does not ensure approval by any regulatory authority outside the U.S. and vice versa.

Even if we or our collaborators obtain regulatory approvals, our marketed products will be subject to ongoing regulatory oversight. If we or our collaborators fail to comply with continuing U.S. and foreign requirements, our approvals could be limited or withdrawn, we could be subject to other penalties, and in any such case our business would be seriously harmed.

Following any initial regulatory approval of a product we or our collaborators may develop, including our four approved products, we will be subject to continuing regulatory oversight, including the review of adverse drug experiences and clinical results that are reported after our drug products are made commercially available. This includes results from any post-marketing tests or surveillance to monitor the safety and efficacy of our approved products or other products required as a condition of approval or otherwise agreed to by us. The regulatory approvals that we receive for ONPATTRO, AMVUTTRA, GIVLAARI and OXLUMO, as well as any regulatory approvals we receive for any of our product candidates, may also be subject to limitations on the approved uses for which the product may be marketed, including any expanded label for AMVUTTRA. Other ongoing regulatory requirements include, among other things, submissions of safety and other post-marketing information and reports, registration and listing, as well as continued compliance with good practice quality guidelines and regulations, including cGMP requirements and GCP requirements for any clinical trials that we conduct post-approval. In addition, we are conducting, and intend to continue to conduct, clinical trials for our product candidates, and we intend to seek approval to market our product candidates, in jurisdictions outside of the U.S., and therefore will be subject to, and must comply with, regulatory requirements in those jurisdictions.

The FDA has significant post-market authority, including, for example, the authority to require labeling changes based on new safety information and to require post-market studies or clinical trials to evaluate serious safety risks related to the use of a product and to require withdrawal of the product from the market. The FDA also has the authority to require a REMS plan after approval, which may impose further requirements or restrictions on the distribution or use of an approved product. As our approved products are used commercially, we or others could identify previously unknown side effects or known side effects could be observed as being more frequent or severe than in clinical studies or earlier post-marketing periods, in which case:

- sales of our approved products may be lower than originally anticipated;
- regulatory approvals for our approved products may be restricted or withdrawn;
- we may decide, or be required, to send product warning letters or field alerts to physicians, pharmacists and hospitals;
- additional nonclinical or clinical studies, changes in labeling, adoption of a REMS plan, or changes to manufacturing processes, specifications and/or facilities may be required; and/or
- government investigations or lawsuits, including class action suits, may be brought against us.

Any of the above occurrences could reduce or eliminate sales of our approved products, increase our expenses and impair our ability to successfully commercialize one or more of these products.

The CMO and manufacturing facilities we use to make our approved products and certain of our current product candidates, including our Cambridge facility, our Norton facility, as well as facilities at Agilent and other CMOs, will also be subject to periodic review and inspection by the FDA and other regulatory agencies. For example, Agilent and our Cambridge-based facility were subject to regulatory inspection by the FDA and the EMA in connection with the review of our applications for regulatory approval for ONPATTRO and GIVLAARI, and may be subject to similar inspection in connection with any subsequent applications for regulatory approval of one or more of our products filed in other territories. The discovery of any new or previously unknown problems with our or our CMO's manufacturing processes or facilities, may result in restrictions on the drug or CMO or facility, including delay in approval or, in the future, withdrawal of the product from the market. For example, due to a routine inspection by the FDA at a CMO facility that resulted in a pending inspection classification, we amended our regulatory submission for vutrisiran, which delayed our PDUFA goal date and AMVUTTRA's FDA approval. Although we have developed cGMP capabilities and processes for the manufacture of patisiran formulated bulk drug product for commercial use and in 2020 completed construction of a cGMP manufacturing facility for drug substance for clinical and, eventually, commercial use, we may not have the ability or capacity to manufacture material at a broader commercial scale in the future. We may manufacture clinical trial materials, or we may contract a third party to manufacture this material for us. Reliance on CMOs entails risks to which we would not be subject if we manufactured products ourselves, including reliance on the applicable CMO for regulatory compliance.

If we or our collaborators, CMOs or service providers fail to comply with applicable continuing regulatory requirements in the U.S. or foreign jurisdictions in which we seek to market our products, we or they may be subject to, among other things,

fining, warning letters, holds on clinical trials, refusal by the FDA or foreign regulatory authorities to approve pending applications or supplements to approved applications, suspension or withdrawal of regulatory approval, product recalls and seizures, refusal to permit the import or export of products, operating restrictions, injunction, civil penalties and criminal prosecution.

We may incur significant liability if enforcement authorities allege or determine that we are engaging in commercial activities with respect to our unapproved product candidates or promoting our commercially approved products in a way that violates applicable regulations.

Physicians have the discretion to prescribe approved drug products for uses that are not described in the product's labeling and that differ from those approved by the FDA or other applicable regulatory agencies. Off-label uses are common across medical specialties. Although the FDA and other regulatory agencies that approve drug products do not regulate a physician's practice of medicine or choice of treatments, the FDA and other regulatory agencies regulate a manufacturer's communications regarding off-label use and prohibit off-label promotion, as well as the dissemination of false or misleading labeling or promotional materials, including by their agents. Manufacturers and their agents may not promote drugs for off-label uses or provide information in the promotion of drug products that is not consistent with the approved labeling for those products. For example, we may not currently promote ONPATTRO or AMVUTTRA in the U.S. for use in any indications other than the treatment of hATTR amyloidosis with polyneuropathy in adults. The FDA and other regulatory and enforcement authorities actively enforce laws and regulations prohibiting promotion of off-label uses and the promotion of products for which marketing approval has not been obtained, and if in the future we are found to have improperly marketed or promoted any of our commercial products, we may be subject to a broad range of civil, administrative and criminal penalties, including injunctive relief related to such commercial products' promotional activities, substantial fines or penalties, and other legal or equitable sanctions. Any adverse decision, finding, allegation, or exercise of enforcement or regulatory discretion could harm our business, prospects, operating results, and financial condition. Other internal or government investigations or legal or regulatory proceedings, including lawsuits brought by private litigants, may also follow as a consequence.

Notwithstanding regulations related to product promotion, the FDA and other regulatory authorities allow companies to engage in truthful, non-misleading and non-promotional scientific exchange concerning their products, and we intend to engage in medical education activities and communicate with healthcare providers in compliance with all applicable laws and regulatory guidance. Nonetheless, the FDA, other applicable regulatory authorities, competitors, and other third parties may take the position that we are not in compliance with such regulations, and if such non-compliance is proven, it could harm our reputation or divert financial and management resources from our core business, and would have a material adverse effect on our business, prospects, operating results or financial condition. Moreover, any threatened or actual government enforcement actions or lawsuits by third parties could also generate adverse publicity, which could decrease demand for our products and require that we devote substantial resources that otherwise could be used productively on other aspects of our business.

In addition to our medical education efforts, we also offer patient support services to assist patients receiving treatment with our commercially approved products. Manufacturers have increasingly become the focus of government investigation of patient support programs based on allegations that through such services illegal inducements are provided to physicians and/or patients, leading to improper utilization of government resources through Medicare, Medicaid and other government programs. Companies that are found to have violated laws such as the federal Anti-Kickback Statute and/or the federal False Claims Act, or FCA, face significant liability, including civil and administrative penalties, criminal sanctions, and potential exclusion from participation in government programs.

As described below, we remain focused on our global compliance program, which is designed to support the execution of these programs and activities in compliance with applicable laws.

Even if we or our collaborators receive regulatory approval to market our product candidates, the market may not be receptive to our product candidates upon their commercial introduction, which could adversely affect our business, prospects, operating results and financial condition.

The product candidates that we are developing are based upon new technologies or therapeutic approaches. Key participants in pharmaceutical marketplaces, such as physicians, third-party payors and consumers, may not accept a product intended to improve therapeutic results based on RNAi technology. As a result, it may be more difficult for us to convince the medical community and third-party payors to accept and use our products, or to provide favorable reimbursement.

Other factors we believe will materially affect market acceptance of our products include:

- the timing of our receipt of any marketing approvals, the terms of any approvals and the countries in which approvals are obtained;
- the safety and efficacy of our product candidates, as demonstrated in clinical trials and as compared with alternative treatments, if any;
- relative convenience, dosing regimen and ease of administration of our product candidates;

- the willingness of patients to accept potentially new routes of administration or new or different therapeutic approaches and mechanisms of action;
- the success of our physician education programs;
- the availability of adequate government and third-party payor reimbursement;
- the pricing of our products, particularly as compared to alternative treatments, and the market perception of such prices and any price increase that we may implement in the future; and
- availability of alternative effective treatments for the diseases that our product candidates we develop are intended to treat and the relative risks, benefits and costs of those treatments.

For example, ONPATTRO utilizes an intravenous mode of administration with pre-medication that physicians and/or patients may not readily adopt, and which may not compete favorably with other available options for the treatment of hATTR amyloidosis with polyneuropathy in adults, including inotersen, marketed by Ionis in several countries, which is administered subcutaneously, or tafamidis, marketed by Pfizer in several countries, which is in pill form. In addition, fitusiran represents a new approach to treating hemophilia which may not be readily accepted by physicians and patients and their caregivers. Assuming positive results from the HELIOS-B Phase 3 clinical trial, vutrisiran, if approved for the treatment of ATTR amyloidosis with cardiomyopathy, could face similar challenges in market acceptance.

We are a multi-product commercial company and expect to continue to invest significant financial and management resources to continue to build our marketing, sales, market access and distribution capabilities and further establish our global infrastructure. If we are not able to continue to develop and scale these capabilities, we may not be able to successfully commercialize our current and any future products.

We received our first product approval in August 2018 and have established capabilities for marketing, sales, market access and distribution over the last several years. We currently expect to rely on third parties to launch and market certain of our product candidates in certain geographies, if approved. However, we are commercializing ONPATTRO, AMVUTTRA, GIVLAARI and OXLUMO, and intend to commercialize other product candidates, if approved, on our own globally in major markets. Accordingly, we have developed internal marketing, sales, market access and distribution capabilities as part of our core product strategy initially in the U.S., Europe and Japan, with expansion ongoing globally, which has required, and will continue to require, significant financial and management resources. For those products for which we will perform marketing, sales, market access and distribution functions ourselves, including ONPATTRO, AMVUTTRA, GIVLAARI and OXLUMO, and for future products we successfully develop with respect to which we retain development and commercialization rights, we could face a number of additional risks, including:

- scaling and retaining our global sales, marketing and administrative infrastructure and capabilities;
- hiring, training, managing and supervising our personnel worldwide;
- the cost of further developing, or leveraging an established, marketing or sales force, which may not be justifiable in light of the revenues generated by any particular product and/or in any specific geographic region; and
- our direct sales and marketing efforts may not be successful.

If we are unable to continue to develop and scale our own global marketing, sales, market access and distribution capabilities for our current and any future products, we will not be able to successfully commercialize our products without reliance on third parties.

The patient populations suffering from hATTR amyloidosis with polyneuropathy, AHP and PH1 are small and have not been established with precision. If the actual number of patients suffering from these diseases is smaller than we estimate, or if we fail to raise awareness of these diseases and diagnosis is not improved, our business, prospects, operating results and financial condition may be adversely affected.

Our estimates regarding the potential market size for ONPATTRO, AMVUTTRA, GIVLAARI, OXLUMO or any future products at the time we commence commercialization, may be materially different from the actual market size, including as a result of the indication approved by regulatory authorities, which could result in significant changes in our business plan and may have a material adverse effect on our business, prospects, operating results and financial condition. As is the case with most orphan diseases, if we are unable to successfully raise awareness of these diseases and improve diagnosis, it could have a material adverse effect on our business, prospects, operating results or financial condition, and it will be more difficult or impossible to achieve profitability.

Any products we currently market or may develop in the future may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, thereby harming our business, prospects, operating results and financial condition.

The regulations that govern marketing approvals, coverage, pricing and reimbursement for new drugs vary widely from country to country and are subject to change. Some countries require approval of the sale price of a drug before it can be

marketed. In many countries, the pricing review period begins after marketing authorization or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. We are actively monitoring these regulations as we market and sell our approved products and as several of our product candidates move through late stages of development. However, a number of our product candidates are currently in the earlier stages of development, and we will not be able to assess the impact of such regulations or any changes to such development programs for a number of years. We might also obtain regulatory approval for a product, including one or more of our approved products, in a particular country, but then be subject to price regulations or price controls that delay our commercial launch of the product and/or negatively impact the revenues we are able to generate from the sale of the product in that country and potentially in other countries due to reference pricing.

We believe that the efforts of governments and third-party payors to contain or reduce the cost of healthcare and legislative and regulatory proposals to broaden the availability of healthcare will continue to affect the business and financial condition of pharmaceutical and biopharmaceutical companies. In the U.S., pharmaceutical pricing is subject to both government and public scrutiny and calls for reform, and the U.S. government has continued to focus on legislative and regulatory changes designed to control costs. Specifically, there have been several recent U.S. Congressional inquiries into prescription drugs, and proposed and enacted federal and state legislation and regulations designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. These developments could, directly or indirectly, affect our ability to sell ONPATRO, AMVUTTRA, GIVLAARI, OXLUMO or future products, if approved, at a favorable price.

At the federal level, for example, the Inflation Reduction Act, or IRA, includes several provisions that will impact our business to varying degrees. For example, the IRA may require us to pay rebates if we increase the cost of a Medicare Part B or Part D drug faster than the rate of inflation. In addition, our cost-sharing responsibility for any approved product covered by Medicare Part D could be significantly greater under the newly designed Part D benefit structure compared to the pre-IRA benefit design. Under the IRA's Price Negotiation Program, a FDA approval for vutrisiran for treatment of Stargardt Disease would cause us to lose the orphan exemption for AMVUTTRA from Medicare price negotiation. As a result, in October 2022, we announced we would not pursue a Phase 3 clinical trial to study vutrisiran for treatment of Stargardt Disease. Manufacturers that fail to comply with the IRA may be subject to various penalties, including civil monetary penalties or a potential excise tax. The effect of the IRA on our business and the healthcare industry in general continues to develop and may have additional adverse impacts on our company or our industry. The IRA is anticipated to have significant effects on the pharmaceutical industry and may reduce the prices we can charge and reimbursement we can receive for our products, among other effects.

Furthermore, the Biden administration has indicated that lowering prescription drug prices is a priority, but we do not know the impact of policies established by the Biden administration to lower the prices of prescription drug prices. For example, the Center for Medicare and Medicaid Innovation is developing new models intended to lower drug costs under Medicare and Medicaid, including designing new payment methods for drugs approved via FDA's accelerated approval pathway, creating a list of generic drugs for which the out-of-pocket Part D costs will be capped at \$2 a month per drug, and establishing new approach for administering outcomes-based agreements for cell and gene therapies. We do not know what additional steps the Biden administration may take to attempt to lower prescription drug prices or the impact of such steps. Although a number of these and other proposed measures may require authorization through additional legislation to become effective, and the current U.S. presidential administration may reverse or otherwise change these measures, both the current U.S. presidential administration and Congress have indicated that they will continue to seek new measures to control drug costs.

At the state level, governments have become increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical product pricing. Some of these measures include restricting price, reimbursement, discounts, product access, and marketing; imposing drug price, cost, and marketing disclosure and transparency requirements; permitting importation from other countries; and encouraging bulk purchasing. For example, on January 5, 2024, the FDA authorized Florida's Agency for Health Care Administration's drug importation proposal, the first step toward Florida facilitating importation of certain prescription drugs from Canada. Importation of drugs from Canada and the Most Favored Nation, or MFN, Model may materially and adversely affect the price we receive for any of our commercially approved products. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. We cannot predict what healthcare reform initiatives may be adopted in the future in the U.S. or other foreign countries. Further federal, state and foreign legislative and regulatory developments are likely, and we expect ongoing initiatives in the U.S. to increase pressure on drug pricing. Such reforms could have a material and adverse effect on our anticipated revenues from one or more of our approved products or other product candidates that we may successfully develop and for which we may obtain regulatory approval and may affect our business, prospects, operating results and financial condition and our ability to develop drug candidates.

Our ability to commercialize our approved products or any future products successfully also will depend in part on the extent to which coverage and reimbursement for these products and related treatments will be available from third-party payors

such as government health administration authorities, private health insurers and other organizations. One or more of our approved products and any other products for which we are able to obtain marketing approval may not be considered medically necessary or cost-effective, and the amount reimbursed may be insufficient to allow us to sell such product(s) or any future products on a competitive basis or realize an appropriate return on our investment in product development. There may be significant delays in obtaining coverage for newly approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the FDA or foreign regulatory authorities. Moreover, eligibility for coverage does not imply that any drug will be reimbursed in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution or that covers a particular provider's cost of acquiring the product. Interim payments for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement may be based on lower-cost drugs that are already marketed, covered, and reimbursed, may be incorporated into existing payments for other services, and may reflect budgetary constraints or imperfections in data. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the U.S. In particular, governments in certain markets such as in EU, the U.K., Japan, and China, provide healthcare at low (or zero) direct costs to consumers at the point of care, and thus have significant power as large single payers to regulate prices or impose other cost control mechanisms. In addition, the emphasis on managed care in the U.S. has increased and we expect will continue to exert downward pressure on pharmaceutical pricing. Coverage policies, third-party reimbursement rates and pharmaceutical pricing regulations may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Increasingly, the third-party payors who reimburse patients or healthcare providers, such as government and private insurance plans, are requiring that drug companies provide them with predetermined discounts from list prices, and are seeking to reduce the prices charged or the amounts reimbursed for drug products. In the U.S., we have entered into over 40 value-based agreements, or VBAs, and are negotiating additional VBAs with commercial health insurers. The goal of these agreements is to ensure that we are paid based on the ability of our commercially approved products to deliver results in the real world setting comparable to those demonstrated in our clinical trials, and the agreements are structured to link the performance of our approved products in real-world use to financial terms. Partnering with payors on these agreements is also intended to provide more confidence regarding the value of our products and help accelerate coverage decisions for patients. If the payment we receive for our products, or the reimbursement provided for such products, is inadequate in light of our significant development and other costs, or if reimbursement is denied, our return on investment could be adversely affected. In addition, we have stated publicly that we intend to grow through continued scientific innovation rather than arbitrary price increases. Specifically, we have stated that we will not raise the price of any product for which we receive marketing approval over the rate of inflation, as determined by the consumer price index for urban consumers (approximately 3.5% currently) absent a significant value driver. Our patient access philosophy could also negatively impact the revenues we are able to generate from the sale of one or more of our products in the future.

Insurers are increasingly adopting programs and policies that limit access to medications and increase out-of-pocket costs for patients. In the U.S., to help patients access and afford our approved product(s), we may utilize programs to assist them, including patient assistance programs and co-pay coupon programs for eligible patients. It is possible that changes in insurer policies regarding co-pay coupons (such as co-pay accumulator and maximizer programs) and patient assistance programs (such as alternative funding programs) and/or the introduction and enactment of new legislation or regulatory action could restrict or otherwise negatively affect these co-pay coupon programs and patient support programs, which could result in fewer patients using affected products, and therefore could have a material adverse effect on our sales, business, and financial condition.

We are subject to U.S. and certain foreign export and import controls, sanctions, embargoes, anti-corruption laws, and anti-money laundering laws and regulations. Failure to comply with these legal standards could impair our ability to compete in domestic and international markets. We can face criminal liability and other serious consequences for violations, which can harm our business.

We are subject to export control and import laws and regulations, including the U.S. Export Administration Regulations, U.S. Customs regulations, various economic and trade sanctions regulations administered by the U.S. Treasury Department's Office of Foreign Assets Control, and anti-corruption laws, including the U.S. Foreign Corrupt Practices Act of 1977, as amended, the U.S. domestic bribery statute contained in 18 U.S.C. § 201, the U.S. Travel Act, the USA PATRIOT Act, the UK Bribery Act 2010, and other applicable anti-bribery and anti-money laundering laws. Anti-corruption laws are interpreted broadly and prohibit companies and their officers, directors, employees, agents, contractors, and other third-party representatives from directly or indirectly authorizing, promising, offering, providing, soliciting, or receiving payments or anything else of value in order to improperly influence the acts or decisions of recipients in the public or private sector or to secure any other improper advantage to obtain or retain business. From time to time, we may engage third parties to conduct clinical trials outside of the U.S., to sell our products abroad, and/or to obtain necessary permits, licenses, patent registrations, and other regulatory approvals. We have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. We can be held liable for the corrupt or other illegal

activities of agents, contractors, and third-party representatives acting on our behalf, even if we do not explicitly authorize or have actual knowledge of such activities. Any violations of the laws and regulations described above may result in substantial fines and penalties, reputational harm, and other adverse consequences.

We remain focused on these laws and the activities they regulate and, as detailed below, maintain a global compliance program designed to empower our business to operate in compliance with their requirements.

Governments outside the U.S. may impose strict price controls, which may adversely affect our revenues.

The pricing of prescription pharmaceuticals is also subject to governmental control outside the U.S. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of regulatory 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 our product candidates to other available therapies, which is time-consuming and costly. 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.

In some countries, including Member States of the EU, or Japan, the pricing of prescription drugs may be subject to governmental control. Additional countries may adopt similar approaches to the pricing of prescription drugs. In such countries, pricing negotiations with governmental authorities can take considerable time after receipt of regulatory approval for a product. In addition, governments and other stakeholders can put considerable pressure on prices and reimbursement levels, including as part of cost containment measures. Moreover, political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after coverage and reimbursement have been obtained. Reference pricing used by various countries and parallel distribution, or arbitrage between low-priced and high-priced countries, can further reduce prices. We cannot be sure that such prices and reimbursement will be acceptable to us or our collaborators. Publication of discounts by third-party payors or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. If pricing is set at unsatisfactory levels or if reimbursement of our products is unavailable or limited in scope or amount, our revenues from sales by us or our collaborators and the potential profitability of our approved products or any future products in those countries would be negatively affected. We could also suffer impact from tightening pricing controls on account of greater competition from less expensive generic or biosimilar products once patent or other exclusivity expires. Certain governments have adopted policies to switch prescribed products to generic versions to reduce costs.

If we or our collaborators, CMOs or service providers fail to comply with healthcare laws and regulations, or legal obligations related to privacy, data protection and information security, we or they could be subject to enforcement actions, which could negatively impact our ability to develop, market and sell our products and may harm our reputation.

Healthcare providers, physicians, and third-party payors play a primary role in the recommendation and prescription of any products for which we obtain marketing approval. Our existing and future arrangements with third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain our business or financial arrangements and relationships through which we market, sell, and distribute our products. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- The U.S. federal Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, the purchase, lease, order, arrangement, or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. A person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it to have committed a violation. Violations are subject to civil and criminal fines and penalties, imprisonment, and exclusion from government healthcare programs. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal FCA or federal civil money penalties.
- The U.S. federal false claims laws, including the FCA, which prohibit, among other things, individuals or entities from knowingly presenting or causing to be presented, claims for payment by government-funded programs such as Medicare or Medicaid that are false or fraudulent, making, using or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government, or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government. Manufacturers can be held liable under the FCA even when they do not submit claims directly to government payors if they are deemed to “cause” the submission of false or fraudulent claims. The FCA also permits a private individual acting as a “whistleblower” to bring actions on behalf of the federal government alleging violations of the FCA and to share in any monetary recovery. Penalties are three times the amount of the claims in question plus civil monetary penalties.
- The federal civil monetary penalties laws, which impose civil fines for, among other things, the offering or transfer of remuneration to a Medicare or Medicaid beneficiary if the person knows or should know it is likely to influence the

beneficiary's selection of a particular provider, practitioner, or supplier of services reimbursable by Medicare or Medicaid, unless an exception applies.

- The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created, among other provisions, federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and, in any matter involving a health care benefit program, knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items or services. Similar to the federal Anti-Kickback Statute, a person or entity can be found guilty of violating HIPAA without actual knowledge of the statute or specific intent to violate it.
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, including its implementing regulations, which impose requirements relating to the privacy, security, and transmission of individually identifiable health information; and requires notification to affected individuals and regulatory authorities of certain breaches of security of individually identifiable health information.
- Federal “sunshine” requirements imposed by the Affordable Care Act on drug, device, biological and medical supply manufacturers when payment is available under Medicare, Medicaid or the Children’s Health Insurance Program (with certain exceptions) to report annually to Health and Human Services under the Open Payments Program, information regarding any payment or other “transfer of value” made or distributed to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), certain non-physician providers such as physician assistants and nurse practitioners, and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit timely, accurate and complete information may result in civil monetary penalties.
- Federal price reporting laws, which require manufacturers to calculate and report complex pricing metrics to government programs, where such reported prices may be used in the calculation of reimbursement and/or discounts on approved products.
- Federal statutory and regulatory requirements applicable to pricing and sales of products to federal government agencies.
- Federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.
- State and foreign laws comparable to each of the above federal laws, including in the EU laws prohibiting giving healthcare professionals any gift or benefit in kind as an inducement to prescribe our products, national transparency laws requiring the public disclosure of payments made to healthcare professionals and institutions, and data privacy laws, in addition to anti-kickback and false claims laws applicable to commercial insurers and other non-federal payors, requirements for mandatory corporate regulatory compliance programs, and laws relating to government reimbursement programs, patient data privacy and security.
- European privacy laws including Regulation 2016/679, known as the General Data Protection Regulation, or the EU GDPR, and the EU GDPR as transposed into the laws of the UK, the UK GDPR, collectively referred to as the GDPR, and the e-Privacy Directive (2002/58/EC), and the national laws implementing each of them, as well as the Public and Electronic Communications Regulations 2003 in the UK and the privacy laws of Japan, Brazil and other territories.
- The California Consumer Privacy Act of 2018, as amended by the California Privacy Rights Act of 2020, or, collectively, the CCPA, that, among other provisions, gives California residents rights of access, correction, portability, and deletion of their personal information and various opt out rights. The CCPA also imposes various obligations on regulated businesses, such as to maintain privacy notices, implement reasonable security practices, and include specific terms in contracts with data processors. The CCPA also created a new state agency that is vested with authority to implement (including through rule making) and enforce the CCPA. The CCPA provides for civil penalties for violations, as well as a limited private right of action for data breaches.
- Furthermore, comprehensive privacy laws similar to the CCPA have been enacted in more than ten other states and proposed in several others. Three states have additionally enacted laws regulating “consumer health data,” which impose additional obligations on regulated entities beyond state comprehensive privacy laws, such as to obtain distinct consents for certain collection and sharing of consumer health data, obtain authorization to sell consumer health data, and maintain a consumer health data privacy policy. Washington’s law regulating consumer health data contains a private right of action. The effects of the CCPA and other state privacy laws are potentially significant and may require us to modify our data collection or processing practices and policies and to incur substantial costs and expenses in an effort to comply and increase our potential exposure to regulatory enforcement and/or litigation.

Some state laws also require pharmaceutical manufacturers to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, in addition to requiring manufacturers to report information related to payments to physicians and other healthcare providers or marketing expenditures and pricing information. State and foreign laws also govern the privacy and security of health information, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating our compliance efforts.

If our operations are found to be in violation of any of the aforementioned requirements, we may be subject to penalties, including civil or criminal penalties (including individual imprisonment), criminal prosecution, monetary damages, the curtailment or restructuring of our operations, or exclusion from participation in government contracting, healthcare reimbursement or other government programs, including Medicare and Medicaid, or the imposition of a corporate integrity agreement with the Office of Inspector General of the Department of Health and Human Services, or the OIG, any of which could materially and adversely affect our business, prospects, operating results or financial condition. We remain focused on enhancing our global compliance infrastructure following the commercial launch of our four products over the last four years in the U.S., EU and multiple other geographies, and as we prepare for the launch of our products in additional countries, assuming regulatory approvals. Although effective compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, these risks cannot be entirely eliminated. For additional information, see the Risk Factor captioned "We may incur significant liability if enforcement authorities allege or determine that we are engaging in commercial activities with respect to our unapproved product candidates or promoting our commercially approved products in a way that violates applicable regulations." Any action against us for an alleged or suspected violation could cause us to incur significant legal expenses and could divert our management's attention from the operation of our business, even if our defense is successful. In addition, achieving and sustaining compliance with applicable laws and regulations may be costly to us in terms of money, time and resources.

If we or our collaborators, CMOs or service providers fail to comply with applicable federal, state or foreign laws or regulations, we could be subject to enforcement actions, which could affect our ability to develop, market and sell our approved products, or any future products, successfully and could harm our reputation and lead to reduced acceptance of our products by the market. These enforcement actions include, among others, civil and criminal penalties, up to and including criminal prosecution resulting in fines, exclusion from healthcare reimbursement programs and imprisonment.

Moreover, federal, state and foreign laws or regulations are subject to change, and while we, our collaborators, CMOs and/or service providers currently may be compliant, we could fall out of compliance due to changes in interpretation, prevailing industry standards or the legal structure.

Third party patient assistance programs that receive financial support from companies have become the subject of enhanced government and regulatory scrutiny. The OIG has established guidelines that suggest that it is lawful for pharmaceutical manufacturers to make donations to charitable organizations who provide co-pay assistance to Medicare patients, provided that such organizations, among other things, are bona fide charities, are entirely independent of and not controlled by the manufacturer, provide aid to applicants on a first-come basis according to consistent financial criteria and do not link aid to use of a donor's product. However, donations to patient assistance programs have received negative publicity and have been the subject of multiple government enforcement actions, related to allegations regarding their use to promote branded pharmaceutical products over other less costly alternatives. Specifically, in recent years, there have been multiple settlements resulting from government claims challenging the legality of patient assistance programs under a variety of federal and state laws. We have made and may continue to make grants to independent charitable foundations that help financially needy patients with their premium, co-pay, and co-insurance obligations. If we do so, and if we or our donation recipients are deemed to be acting in violation of relevant laws, regulations or evolving government guidance, we could be subject to damages, fines, penalties, or other criminal, civil, or administrative sanctions or enforcement actions.

We are subject to governmental regulation and other legal obligations related to privacy, data protection and information security, and we are subject to consumer protection laws that regulate our marketing practices and prohibit unfair or deceptive acts or practices. Our actual or perceived failure to comply with such obligations could harm our business.

The GDPR imposes strict requirements on controllers and processors of personal data, including special protections for "special category data," which includes health, biometric and genetic information of data subjects located in the EEA and UK. Further, GDPR provides a broad right for EEA Member States to create supplemental national laws, such as laws relating to the processing of health, genetic and biometric data, which could further limit our ability to use and share such data or could cause our costs to increase, and harm our business and financial condition.

Failure to comply with the requirements of the GDPR and the related national data protection laws of the EEA Member States and the UK, which may deviate slightly from the GDPR, may result in fines of up to 4% of total global annual revenue, or €20.0 million (£17.5 million under the UK GDPR), whichever is greater, and in addition to such fines, we may be the subject of litigation and/or adverse publicity, which could have a material adverse effect on our reputation and business. As a result of the implementation of the GDPR, we are required to implement a number of measures to ensure compliance with the data protection regime. The GDPR (i) requires us to inform data subjects of how we process their personal data and how they can exercise their rights, (ii) requires us to ensure we have a valid legal basis to process personal data (if this is consent, the

requirements for obtaining consent carries a higher threshold), (iii) requires us to appoint a data protection officer where sensitive personal data (i.e., health data) is processed on a large scale, (iv) introduces mandatory data breach notification requirements throughout the EEA and UK, (v) requires us to maintain records of our processing activities and document data protection impact assessments where there is high risk processing, (vi) imposes additional obligations on us when we are contracting with service providers, requires (vii) appropriate technical and organizational measures to be put in place to safeguard personal data and (viii) requires us to adopt appropriate privacy governance including policies, procedures, training and data audit.

Significantly, the GDPR imposes strict rules on the transfer of personal data out of the EEA and UK to the U.S. or other regions that have not been deemed to offer “adequate” privacy protections. In the past, companies in the U.S. were able to rely upon the EU-U.S., UK-U.S. and the Swiss-U.S. Privacy Shield frameworks as a basis for lawful transfer of personal data from the EU and the UK to the U.S. In July 2020, the Court of Justice of the European Union, or CJEU, in Case C-311/18 (Data Protection Commissioner v Facebook Ireland and Maximilian Schrems, or Schrems II) invalidated the EU-U.S. Privacy Shield on the grounds that the Privacy Shield failed to offer adequate protections to EU personal data transferred to the U.S. The CJEU, in the same decision, deemed that the Standard Contractual Clauses, or SCCs, published by the EC are valid. However, the CJEU ruled that transfers made pursuant to the SCCs need to be assessed on a case-by-case basis to ensure the law in the recipient country provides “essentially equivalent” protections to safeguard the transferred personal data as the EU, and required businesses to adopt supplementary measures if such standard is not met. Subsequent guidance published by the European Data Protection Board, or EDPB, in June 2021 described what such supplementary measures must be, and stated that businesses should avoid or cease transfers of personal data if, in the absence of supplementary measures, equivalent protections cannot be afforded. On June 4, 2021, the EC published new versions of the SCCs, which seek to address the issues identified by the CJEU’s Schrems II decision and provide further details regarding the transfer assessments that the parties are required to conduct when implementing the new SCCs. However, there continue to be concerns about whether the SCCs and other mechanisms will face additional challenges. Similarly, in September 2020, the Swiss data protection authority determined the Swiss-U.S. Privacy Shield framework was no longer a valid mechanism for Swiss-U.S. data transfers and raised questions about the validity of the SCCs as a mechanism for transferring personal data from Switzerland. While SCCs provide an alternative to our Privacy Shield certification for EU-U.S. data flows, the decision (and certain regulatory guidance issued in its wake) casts doubt on the legality of EU-U.S. data flows in general. Any inability to transfer, or burdensome restrictions on the ability to transfer, personal data from the EU to the U.S. in compliance with applicable data protection laws may impede our ability to conduct clinical trials and may adversely affect our business, prospects, operating results and financial condition. The UK is not subject to the EC’s new SCCs but has published its own transfer mechanism, the International Data Transfer Agreement or International Data Transfer Addendum, which enables transfers from the UK. On March 25, 2022, the EC and the U.S. announced a political agreement on a new “Trans-Atlantic Data Privacy Framework” to replace the invalidated Privacy Shield. The framework introduced new binding safeguards to address the concerns raised by the CJEU in Schrems II. On July 10, 2023, the EC announced that it had adopted its adequacy decision for that data privacy framework, labelled the EU-U.S. Data Privacy Framework. The adequacy decision concluded that the U.S. ensures an adequate level of protection for personal data transferred from the EU to US companies under the new framework, and the EC stated that as a result personal data can flow safely from the EU to US companies participating in the framework, without having to put in place additional data protection safeguards. The EU-U.S. Data Privacy Framework is subject to periodic reviews, to be conducted by the EC, together with other European data protection authorities and U.S. authorities, with the first review to take place within a year of adoption of the adequacy decision. A case has been lodged with and remains pending before the EU courts challenging the validity of the EU-U.S. Data Privacy Framework.

EEA Member States have adopted implementing national laws to implement the GDPR which may partially deviate from the GDPR and the competent authorities in the EEA Member States may interpret GDPR obligations slightly differently from country to country, and we do not expect to operate in a uniform legal landscape in the EU. In addition, the UK Government has now introduced a Data Protection and Digital Information Bill, or the UK Bill, into the UK legislative process. The aim of the UK Bill is to reform UK’s data protection regime following Brexit. If passed, the final version of the UK Bill may have the effect of further altering the similarities between the UK and EEA data protection regime. The anticipated UK general election in 2024 could postpone passage of the UK Bill.

We are subject to the supervision of local data protection authorities in those jurisdictions in which we are monitoring the behavior of individuals in the EEA or UK (i.e., undertaking clinical trials). We depend on a number of third parties in relation to the provision of our services, a number of which process personal data of EU and/or UK individuals on our behalf. With each such provider we enter or intend to enter into contractual arrangements under which the provider is contractually obligated to only process personal data according to our instructions, and conduct or intend to conduct diligence to ensure that they have sufficient technical and organizational security measures in place.

We are also subject to evolving European privacy laws on electronic marketing and cookies. The EU is in the process of replacing the e-Privacy Directive (2002/58/EC) with a new set of rules taking the form of a regulation, which will be directly implemented in the laws of each European member state, without the need for further enactment. While the e-Privacy Regulation was originally intended to be adopted on May 25, 2018 (alongside the GDPR), it is still going through the European legislative process. Draft regulations were rejected by the Permanent Representatives Committee of the Council of EU on

November 22, 2019; it is not clear when, or even if, new regulations will be adopted. We are also subject to current and evolving privacy laws in other foreign countries, such as Canada.

Compliance with U.S. and international data protection laws and regulations requires that we take on more onerous obligations in our contracts, restrict our ability to collect, use and disclose data, and, in some cases, impacts our ability to operate in certain jurisdictions. Failure to comply with these laws and regulations could result in government enforcement actions (which could include civil, criminal and administrative penalties), private litigation, and/or adverse publicity and could negatively affect our operating results and business. Moreover, clinical trial subjects, employees and other individuals about whom we or our potential collaborators obtain personal information, as well as the providers who share this information with us, may limit our ability to collect, use and disclose the information. Claims that we have violated individuals' privacy rights, failed to comply with data protection laws, or breached our contractual obligations, even if we are not found liable, could be expensive and time-consuming to defend and could result in adverse publicity that could harm our business.

Our ability to obtain services, reimbursement or funding from the federal government may be impacted by possible reductions in federal spending and services, and any inability on our part to effectively adapt to such changes could substantially affect our business, prospects, operating results and financial condition.

Under the Budget Control Act of 2011, the failure of Congress to enact deficit reduction measures of at least \$1.2 trillion for the years 2013 through 2021 triggered automatic cuts to most federal programs. These cuts included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, starting in 2013. Certain of these automatic cuts have been implemented resulting in reductions in Medicare payments to physicians, hospitals, and other healthcare providers, among other things. Due to legislation amending the statute, including the Bipartisan Budget Act of 2018, these reductions will stay in effect through 2030 unless additional Congressional action is taken. Pursuant to the Coronavirus Aid, Relief, and Economic Security Act, as well as subsequent legislation, these reductions were suspended from May 1, 2020 through December 31, 2021 due to the COVID-19 pandemic. Following the suspension, a 1% payment reduction began on April 1, 2022, lasting through June 30, 2022. The 2% payment reduction resumed on July 1, 2022. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for our approved products or any of our product candidates for which we may obtain regulatory approval, or the frequency with which our products or any future product is prescribed or used.

Previous actions taken by Congress to reduce spending, disagreements in Congress over government funding levels, high-levels of government debt, and the Medicare Trustees' warnings about the programs' sustainability as presently structured suggest that uninterrupted/continued growth in funding for relevant programs is not guaranteed. Amounts allocated to federal grants and contracts may be reduced or eliminated. These reductions may also impact the ability of relevant agencies to timely review and approve drug research and development, manufacturing, and marketing activities, which may delay our ability to develop, market and sell our approved products and any other products we may develop.

If we fail to comply with our obligations under the 340B Drug Pricing Program or other U.S. governmental pricing programs, we could be subject to additional reimbursement requirements, penalties, sanctions and fines, which could have a material adverse effect on our business, prospects, operating results and financial condition.

We participate in the 340B Drug Pricing Program, Medicaid Drug Rebate Program, and a number of other federal and state government pricing programs in the U.S. in order to obtain coverage for our products by certain government health care programs. These programs generally require that we provide discounts or pay rebates to certain payers when our products are dispensed to beneficiaries of these programs. These programs may also impose other requirements, including certain price reporting requirements. Changes to our obligations under these government pricing programs occur frequently and program requirements are often ambiguous. We may be or become subject to penalties as a result of our failure to comply with obligations under these programs, including if we fail to provide timely and accurate information to the government, to pay the correct rebates, or to offer the correct discounted pricing. Complying with these programs and future changes to these programs can be cost-and resource-intensive and could have a material adverse effect on our business, prospects, operating results and financial condition.

There is a substantial risk of product liability claims in our business. If we are unable to obtain sufficient insurance, a product liability claim against us could adversely affect our business, prospects, operating results and financial condition.

Our business exposes us to significant potential product liability risks that are inherent in the development, testing, manufacturing and marketing of human therapeutic products. Product liability claims could delay or prevent completion of our clinical development programs. Such claims might not be fully covered by product liability insurance. In addition, product liability claims could result in an FDA investigation of the safety and effectiveness of our approved products, our manufacturing processes and facilities or our marketing programs, and potentially a recall of our products or more serious enforcement action, limitations on the approved indications for which they may be used, or suspension or withdrawal of approvals. Regardless of the merits or eventual outcome, liability claims may also result in decreased demand for our products, injury to our reputation, costs to defend the related litigation, a diversion of management's time and our resources, substantial

monetary awards to trial participants or patients and a decline in our stock price. We currently have product liability insurance that we believe is appropriate for our stage of development, including the marketing and sale of our approved products. Any insurance we have or may obtain may not provide sufficient coverage against potential liabilities. Furthermore, clinical trial and product liability insurance is becoming increasingly expensive. As a result, we may be unable to obtain sufficient insurance at a reasonable cost to protect us against losses caused by product liability claims that could have a material adverse effect on our business.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements or insider trading violations, which could significantly harm our business, prospects, operating results and financial condition.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with governmental regulations, including healthcare fraud and abuse and anti-kickback laws and regulations in the U.S. and abroad, or failure to 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. As discussed in the Risk Factor captioned “If we or our collaborators, CMOs or service providers fail to comply with healthcare laws and regulations, or legal obligations related to privacy, data protection and information security, we or they could be subject to enforcement actions, which could negatively impact our ability to develop, market and sell our products and may harm our reputation,” these laws and regulations may 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 improper trading based upon, information obtained in the course of clinical studies, which could result in regulatory sanctions and serious harm to our reputation. We maintain a global compliance program and remain focused on its evolution and enhancement. Our program includes efforts such as risk assessment and monitoring, fostering a speak-up culture encouraging employees and third parties to raise good faith questions or concerns, and defined processes and systems for reviewing and remediating allegations and identified potential concerns. It is not always possible, however, to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective 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, prospects, operating results and financial condition, including the imposition of significant fines or other sanctions.

If we do not comply with laws regulating the protection of the environment and health and human safety, our business, prospects, operating results and financial condition could be adversely affected.

Our research, development and manufacturing involve the use of hazardous materials, chemicals and various radioactive compounds. We maintain quantities of various flammable and toxic chemicals in our facilities in Cambridge and Norton that are required for our research, development and manufacturing activities. We are subject to federal, state and local laws and regulations governing the use, manufacture, storage, handling and disposal of these hazardous materials. We believe our procedures for storing, handling and disposing these materials in our Cambridge and Norton facilities comply with the relevant guidelines of the City of Cambridge, the town of Norton, the Commonwealth of Massachusetts and the Occupational Safety and Health Administration of the U.S. Department of Labor. Although we believe that our safety procedures for handling and disposing of these materials comply with the standards mandated by applicable regulations, the risk of accidental contamination or injury from these materials cannot be eliminated. If an accident occurs, we could be held liable for resulting damages, which could be substantial. We are also subject to numerous environmental, health and workplace safety laws and regulations, including those governing laboratory procedures, exposure to blood-borne pathogens and the handling of biohazardous materials.

Although we maintain workers’ compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of these materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials. Additional federal, state and local laws and regulations affecting our operations may be adopted in the future. We may incur substantial costs to comply with, and substantial fines or penalties if we violate, any of these laws or regulations.

Risks Related to Patents, Licenses and Trade Secrets

If we are not able to obtain and enforce patent protection for our discoveries, our ability to develop and commercialize our product candidates will be harmed.

Our success depends, in part, on our ability to protect proprietary compositions, methods and technologies that we develop under the patent and other intellectual property laws of the U.S. and other countries, so that we can prevent others from unlawfully using our inventions and proprietary information. However, we may not hold proprietary rights to some patents required for us to manufacture and commercialize our proposed products. Because certain U.S. patent applications are confidential until the patents issue, such as applications filed prior to November 29, 2000, or applications filed after such date

which will not be filed in foreign countries, third parties may have filed patent applications for subject matter covered by our pending patent applications without our being aware of those applications, and our patent applications may not have priority over those applications. For this and other reasons, we may be unable to secure desired patent rights, thereby losing desired exclusivity. Further, we or our collaborators may be required to obtain licenses under third-party patents to market one or more of our or our collaborator's approved products, or further develop and commercialize future products, or continue to develop product candidates in our pipeline being developed by us or our collaborators. If licenses are not available to us or not available on reasonable terms, we or our licensees may not be able to market the affected products or conduct the desired activities.

Our strategy depends on our ability to rapidly identify and seek patent protection for our discoveries. In addition, we may rely on third-party collaborators to file patent applications relating to proprietary technology that we develop jointly as part of collaborations. The process of obtaining patent protection is expensive and time-consuming. If we or our present or future collaborators fail to file and prosecute all necessary and desirable patent applications at a reasonable cost and in a timely manner, our business may be adversely affected. Despite our efforts and the efforts of our collaborators to protect our proprietary rights, unauthorized parties may be able to obtain and use information that we regard as proprietary. While issued patents are presumed valid, this does not guarantee that the patent will survive a validity challenge or be held enforceable. Any patents we have obtained, or obtain in the future, may be challenged, invalidated, adjudged unenforceable or circumvented by parties attempting to design around our intellectual property. Moreover, third parties or the United States Patent and Trademark Office, or USPTO, may commence interference proceedings involving our patents or patent applications. Any challenge to, finding of unenforceability or invalidation or circumvention of, our patents or patent applications, would be costly, would require significant time and attention of our management, could reduce or eliminate milestone and/or royalty payments to us from third party licensors and could have a material adverse effect on our business.

Our pending patent applications may not result in issued patents. The patent position of pharmaceutical or biotechnology companies, including ours, is generally uncertain and involves complex legal and factual considerations. The standards that the USPTO and its foreign counterparts use to grant patents are not always applied predictably or uniformly and can change. Similarly, the ultimate degree of protection that will be afforded to biotechnology inventions, including ours, in the U.S. and foreign countries, remains uncertain and is dependent upon the scope of the protection decided upon by patent offices, courts and lawmakers. Moreover, there are periodic discussions in the U.S. Congress and in international jurisdictions about modifying various aspects of patent law. For example, the America Invents Act, or AIA, included a number of changes to the patent laws of the U.S. If any of the enacted changes do not provide adequate protection for discoveries, including our ability to pursue infringers of our patents for substantial damages, our business could be adversely affected. One major provision of the AIA, which took effect in March 2013, changed U.S. patent practice from a first-to-invent to a first-to-file system. If we fail to file an invention before a competitor files on the same invention, we no longer have the ability to provide proof that we were in possession of the invention prior to the competitor's filing date, and thus would not be able to obtain patent protection for our invention. There is also no uniform, worldwide policy regarding the subject matter and scope of claims granted or allowable in pharmaceutical or biotechnology patents.

Accordingly, we do not know the degree of future protection for our proprietary rights or the breadth of claims that will be allowed in any patents issued to us or to others. We also rely to a certain extent on trade secrets, know-how and technology, which are not protected by patents, to maintain our competitive position. If any trade secret, know-how or other technology not protected by a patent were to be disclosed to or independently developed by a competitor, our business, prospects, operating results and financial condition could be materially adversely affected.

Failure to obtain and maintain broad patent scope and all available regulatory exclusivities and to maximize patent term restoration or extension on patents covering our product candidates and products may lead to loss of exclusivity and generic entry resulting in a loss of market share and/or revenue.

We license patent rights from third-party owners. If such owners do not properly or successfully obtain, maintain or enforce the patents underlying such licenses, our competitive position and business, prospects, operating results and financial condition may be harmed.

We are a party to a number of licenses that give us rights to third-party intellectual property that is necessary or useful for our business. In particular, we have obtained licenses from, among others, Ionis, Arbutus, and Dicerna. We also intend to enter into additional licenses to third-party intellectual property in the future.

Our success will depend in part on the ability of our licensors to obtain, maintain and enforce patent protection for our licensed intellectual property, in particular, those patents to which we have secured exclusive rights. Our licensors may not successfully prosecute the patent applications we have licensed. Even if patents issue in respect of these patent applications, our licensors may fail to maintain these patents, may determine not to pursue litigation against other companies that are infringing these patents, or may pursue such litigation less aggressively than we would. Without protection for the intellectual property we license, other companies might be able to offer substantially identical products for sale, which could adversely affect our competitive business position and harm our business, prospects, operating results and financial condition. In addition, we sublicense our rights under various third-party licenses to our collaborators. Any impairment of these sublicensed rights could

result in reduced revenues under our collaboration agreements or result in termination of an agreement by one or more of our collaborators.

Other companies or organizations may challenge our patent rights or may assert patent rights that prevent us from developing and commercializing our products.

RNAi is a relatively new scientific field, the commercial exploitation of which has resulted in many different patents and patent applications from organizations and individuals seeking to obtain patent protection in the field. We have obtained grants and issuances of RNAi patents and have licensed many of these patents from third parties on an exclusive basis. The issued patents and pending patent applications in the U.S. and in key markets around the world that we own or license claim many different methods, compositions and processes relating to the discovery, development, manufacture and commercialization of RNAi therapeutics.

Specifically, we have a portfolio of patents, patent applications and other intellectual property covering, among other things: fundamental aspects of the structure and uses of siRNAs, including their use as therapeutics, and RNAi-related mechanisms; chemical modifications to siRNAs that improve their suitability for therapeutic and other uses; siRNAs directed to specific targets as treatments for particular diseases; delivery technologies, such as in the fields of carbohydrate conjugates and cationic liposomes; and all aspects of our specific development candidates.

As the field of RNAi therapeutics is maturing, patent applications are being fully processed by national patent offices around the world. There is uncertainty about which patents will issue, and, if they do, as to when, to whom, and with what claims. It is likely that there will be significant litigation and other proceedings, such as interference, re-examination and opposition proceedings, as well as pre- and post-grant review proceedings in various patent offices relating to patent rights in the RNAi field. In addition, third parties may challenge the validity of our patents. For example, a third party has filed an opposition in the European Patent Office, or EPO, against our owned patent EP 2723758, with claims directed to RNAi compositions and methods for silencing ANGPTL3, arguing that the granted claims are invalid. Following an oral hearing in February 2021, the patent was revoked. A notice of appeal of the EPO's decision was filed in June 2021 and following an oral hearing in November 2023, the appeal was dismissed resulting in the patent remaining revoked. In March 2022, a third party filed an opposition with the EPO against our owned patent EP3105332, which is directed to RNAi compositions and methods for silencing ketoheokinase, seeking to revoke the patent. In addition, in February 2023, a third party filed an opposition with the EPO against our owned patent EP 3366775, titled "Modified RNA Agents" seeking to revoke the patent. Oral hearings are anticipated in these proceedings at times to be determined by the EPO. Additionally, the validity of two Chinese patents (ZL201380063930.5 and ZL201810143112.0) relating to inclisiran were challenged by a third party in China. The China National Intellectual Property Administration recently issued decisions confirming that patent No. ZL201380063930.5 remained valid as a whole, and patent No. ZL201810143112.0 remained valid based on the amended version of the claims we submitted. We expect that additional oppositions will be filed in the EPO and elsewhere, and other challenges will be raised relating to other patents and patent applications in our portfolio. In many cases, the possibility of appeal exists for either us or our opponents, and it may be years before final, unappealable rulings are made with respect to these patents in certain jurisdictions. The timing and outcome of these and other proceedings is uncertain and may adversely affect our business, prospects, operating results and financial condition if we are not successful in defending the patentability and scope of our pending and issued patent claims. Even if our rights are not directly challenged, disputes could lead to the weakening of our intellectual property rights. Our defense against any attempt by third parties to circumvent or invalidate our intellectual property rights could be costly to us, could require significant time and attention of our management and could have a material adverse effect on our business, prospects, operating results and financial condition and on our ability to successfully compete in the field of RNAi.

There are many issued and pending patents that claim aspects of oligonucleotide chemistry and modifications that we may need for our siRNA products marketed by us or our licensees, our late-stage therapeutic candidates being developed by us or our collaborators, including zilebesiran and fitusiran, as well as our other pipeline products. There are also many issued patents that claim targeting genes or portions of genes that may be relevant for siRNA drugs we wish to develop. In addition, there may be issued and pending patent applications that may be asserted against us in a court proceeding or otherwise based upon the asserting party's belief that we may need such patents for our siRNA therapeutic candidates or marketed products, or to further develop and commercialize future products, or to continue to develop candidates in our pipeline that are being developed by us or our collaborators. Thus, it is possible that one or more organizations will hold patent rights to which we may need a license, or hold patent rights which could be asserted against us. If those organizations refuse to grant us a license to such patent rights on reasonable terms or at all and/or a court rules that we need such patent rights that have been asserted against us, we may be unable to market our products, including ONPATTRO, AMVUTTRA, GIVLAARI or OXLUMO, or to perform research and development or other activities covered by such patents. For example, during 2017 and 2018, Silence Therapeutics, plc, or Silence, filed claims in several jurisdictions, including the High Court of England and Wales, and named us and our wholly owned subsidiary Alnylam UK Ltd. as co-defendants. Silence alleged various claims, including that ONPATTRO infringed one or more Silence patents. There were also a number of related actions brought by us or Silence in connection with this intellectual property dispute. In December 2018, we entered into a Settlement and License Agreement with Silence, resolving

all ongoing claims, administrative proceedings, and regulatory proceedings worldwide between us regarding, among other issues, patent infringement, patent invalidity and breach of contract.

If we become involved in intellectual property litigation or other proceedings related to a determination of rights, we could incur substantial costs and expenses, and in the case of such litigation or proceedings against us, substantial liability for damages or be required to stop our product development and commercialization efforts.

Third parties may sue us for infringing their patent rights. For example, in October 2017 Silence sued us in the UK alleging that ONPATTRO and other investigational RNAi therapeutics we or MDCO were developing infringed one or more Silence patents. In December 2018 we and Silence settled all ongoing litigation between us. A third party may also claim that we have improperly obtained or used its confidential or proprietary information.

Furthermore, third parties may challenge the inventorship of our patents or licensed patents. For example, in March 2011, The University of Utah, or Utah, filed a complaint against us, Max Planck Gesellschaft Zur Foerderung Der Wissenschaften e.V. and Max Planck Innovation, together, Max Planck, Whitehead, MIT and the University of Massachusetts, claiming that a professor of Utah was the sole inventor, or in the alternative, a joint inventor of certain of our in-licensed patents. Utah was seeking correction of inventorship of the Tuschl patents, unspecified damages and other relief. After several years of court proceedings and discovery, the court granted our motions for summary judgment and dismissed Utah's state law damages claims. During the pendency of this litigation, as well as the Dicerna litigation described below, we incurred significant costs, and in each case, the litigation diverted the attention of our management and other resources that would otherwise have been engaged in other activities.

We may need to resort to litigation to enforce a patent issued or licensed to us or to determine the scope and validity of proprietary rights of others or protect our proprietary information and trade secrets. For example, during the second quarter of 2015, we filed a trade secret misappropriation lawsuit against Dicerna to protect our rights in the RNAi assets we purchased from Merck Sharp & Dohme Corp., or Merck. In April 2018, we and Dicerna settled all claims in the litigation between us. In March 2022, we announced that we separately filed suit in United States District Court for the District of Delaware against Pfizer and Moderna seeking damages for infringement of U.S. Patent No. 11,246,933, or the '933 patent in the parties' manufacture and sale of their messenger RNA, or mRNA, COVID-19 vaccines. Pfizer joined BioNTech SE, or BioNTech, to the suit and filed counterclaims. In July 2022, we filed an additional lawsuit in United States District Court for the District of Delaware against each of Pfizer/BioNTech and Moderna seeking damages for infringing U.S. Patent No. 11,382,979, or the '979 patent. The court combined the two patents in a single suit for each of Pfizer/BioNTech, or the 2022 Lawsuit, and Moderna with trial dates set for each in November 2024. On May 26, 2023, we filed additional lawsuits against Pfizer and Moderna in Delaware seeking damages for infringing U.S. Patent No. 11,590,229 in the United States District Court for the District of Delaware. In addition to this patent, we added U.S. Patent Nos. 11,633,479 and 11,633,480 in the more recently filed suits against both Pfizer and Moderna and also U.S. Patent No. 11,612,657 against Pfizer only. On August 9, 2023, a Markman hearing was held in the U.S. District Court for the District of Delaware to consider the meaning of three disputed terms as used in the '933 and '979 patents, and on August 21, 2023, the court issued an order construing two of the three terms, and deferred a ruling on the third term pending an evidentiary hearing, which was held on January 4, 2024 with the final ruling deferred pending the outcome of an additional hearing scheduled for July 11-12, 2024. Subsequently, we and Moderna jointly agreed to final judgment of non-infringement of two of our patents, and that judgment was entered by the court on August 30, 2023, and on September 7, 2023, we appealed the claim construction ruling to the Court of Appeals for the Federal Circuit in the 2022 lawsuit against Moderna. The claim construction ruling did not affect one of the patents in the lawsuit filed against Moderna on May 26, 2023, and that case is going forward on a schedule with an anticipated trial date in the latter half of 2025. In September 2023, we and Pfizer/BioNTech agreed to consolidate the 2022 Lawsuit and 2023 lawsuits into one case, which will require moving the trial date from November 2024 to the first half of 2025, with the final schedule to be determined by the court. On January 4, 2024 a hearing was held in the consolidated Pfizer/BioNTech case to construe a final claim term with the final ruling pending. The aforementioned patents relate to our biodegradable cationic lipids that are foundational to the success of the mRNA COVID-19 vaccines.

In protecting our intellectual patent rights through litigation or other means, a third party may claim that we have improperly asserted our rights against them. For example, in August 2017, Dicerna successfully added counterclaims against us in the above-referenced trade secret lawsuit alleging that our lawsuit represented abuse of process and claiming tortious interference with its business. In addition, in August 2017, Dicerna filed a lawsuit against us in the United States District Court of Massachusetts alleging attempted monopolization by us under the Sherman Antitrust Act. As noted above, in April 2018, we and Dicerna settled all claims in the litigation between us.

In addition, in connection with certain license and collaboration agreements, we have agreed to indemnify certain third parties for certain costs incurred in connection with litigation relating to intellectual property rights or the subject matter of the agreements. The cost to us of any litigation or other proceeding relating to such intellectual property rights, even if resolved in our favor, could be substantial, and litigation would divert our management's efforts. Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. Uncertainties resulting from the initiation and continuation of any litigation or legal proceeding could delay our research, development and commercialization efforts and limit our ability to continue our operations.

If any parties successfully claim that our creation or use of proprietary technologies infringes upon or otherwise violates their intellectual property rights, we might be forced to pay damages, potentially including treble damages, if we are found to have willfully infringed on such parties' patent rights. In addition to any damages we might have to pay, a court could issue an injunction requiring us to stop the infringing activity or obtain a license from the claimant. Any license required under any patent may not be made available on commercially reasonable terms, or at all. In addition, such licenses are in many instances non-exclusive and, therefore, our competitors may have access to the same technology that is licensed to us. If we fail to obtain a required license and are unable to design around a patent, we may be unable to effectively market some of our technology and products, which could limit our ability to generate revenues or achieve profitability and possibly prevent us from generating revenue sufficient to sustain our operations. Moreover, we expect that a number of our collaborations will provide that royalties payable to us for licenses to our intellectual property may be offset by amounts paid by our collaborators to third parties who have competing or superior intellectual property positions in the relevant fields, which could result in significant reductions in our revenues from products developed through collaborations.

If we fail to comply with our obligations under any licenses or related agreements, we may be required to pay damages and could lose license or other rights that are necessary for developing, commercializing and protecting our RNAi technology, as well as our approved products and product candidates.

Our current licenses impose, and any future licenses we enter into are likely to impose, various development, commercialization, funding, milestone, royalty, diligence, sublicensing, insurance, patent prosecution and enforcement, and other obligations on us. If we breach any of these obligations, or use the intellectual property licensed to us in an unauthorized manner, we may be required to pay damages and the licensor may have the right to terminate the license or render the license non-exclusive, which could result in us being unable to develop, manufacture, market and sell products that are covered by the licensed technology or enable a competitor to gain access to the licensed technology. Moreover, we could incur significant costs and/or disruption to our business and distraction of our management defending against any breach of such licenses alleged by the licensor. For example, in June 2018, Ionis sent us a notice claiming that it was owed payments under our second amended and restated strategic collaboration and license agreement as a result of the January 2018 restructuring of our collaboration agreement with Sanofi and the related Exclusive TTR License and AT3 License Terms. Ionis claimed it was owed technology access fees, or TAFs, based on rights granted and amounts paid to us in connection with the Sanofi restructuring. Ionis later filed a Demand for Arbitration with the Boston office of the American Arbitration Association against us, asserting, among other things, breach of contract. Upon completion of the arbitration process in the second quarter of 2020, in October 2020, a partial award was issued by the arbitration panel that sought additional information from us. The arbitration panel issued its final award in December 2020, which ruled in favor of Ionis's request for a TAF on certain rights the panel determined we received in the Sanofi restructuring (but rejected the TAF amount sought by Ionis), and in favor of us in denying Ionis's request for a TAF on a milestone payment received by us in the same restructuring. The panel's final award also denied Ionis's request for pre-judgment interest and attorney's fees. Pursuant to the panel's final award, we paid \$41.2 million to Ionis in January 2021.

Moreover, our licensors may own or control intellectual property that has not been licensed to us and, as a result, we may be subject to claims, regardless of their merit, that we are infringing or otherwise violating the licensor's rights. In addition, while we cannot currently determine the amount of the royalty obligations we will be required to pay on sales of each of our approved products or future products, if any, the amounts may be significant. The amount of our future royalty obligations will depend on the technology and intellectual property we use in such products. Therefore, even if we successfully develop and commercialize products, we may be unable to achieve or maintain profitability.

Confidentiality agreements with employees and others may not adequately prevent disclosure of trade secrets and other proprietary information.

In order to protect our proprietary technology and processes, we rely in part on confidentiality agreements with our collaborators, employees, consultants, scientific advisors, CMOs, outside scientific collaborators and sponsored researchers, and other advisors. These agreements may not effectively prevent disclosure of confidential information and may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. In addition, other third parties may independently discover trade secrets and proprietary information, and in such cases we could not assert any trade secret rights against such party. Costly and time-consuming litigation could be necessary to enforce and determine the scope of our proprietary rights, and failure to obtain or maintain trade secret protection could adversely affect our business, prospects, operating results and financial condition.

Risks Related to Competition

The pharmaceutical market is intensely competitive. If we or our collaborators are unable to compete effectively with existing drugs, new treatment methods and new technologies, we or our collaborators may be unable to commercialize successfully any drugs that we or our collaborators develop.

The pharmaceutical market is intensely competitive and rapidly changing. Many large pharmaceutical and biotechnology companies, academic institutions, governmental agencies and other public and private research organizations are pursuing the development of novel drugs for the same diseases that we are targeting or expect to target. Many of our competitors have:

- substantially greater financial, technical and human resources than we have;
- more extensive experience in pre-clinical testing, conducting clinical trials, obtaining regulatory approvals, and in manufacturing, marketing and selling drug products;
- product candidates that are based on previously tested or accepted technologies;
- multiple products that have been approved or are in late stages of development; and
- collaborative arrangements in our target markets with leading companies and research institutions.

We will face intense competition from drugs that have already been approved and accepted by the medical community for the treatment of the conditions for which we may develop drugs. In addition, there are a number of drugs currently under development and that may become commercially available in the future, for the treatment of conditions for which we may try to develop drugs. These drugs may be more effective, safer, less expensive, have more convenient administration or be marketed and sold more effectively, than any products we develop and commercialize.

For example, assuming positive results in our HELIOS-B Phase 3 clinical and regulatory approval, vutrisiran, our RNAi therapeutic in development for treatment of ATTR amyloidosis with cardiomyopathy, would compete with VYNDALAN/VYNDAMAX (tafamidis), marketed by Pfizer, which is currently approved to treat this disease. In addition, BridgeBio announced positive results from its Phase 3 clinical trial of acoramidis, a TTR stabilizer, in ATTR amyloidosis with cardiomyopathy in July 2023, and announced in February 2024 that the FDA accepted its NDA for filing with a PDUFA action date of November 29, 2024. BridgeBio also announced that the European Medicines Agency accepted its marketing authorization application with a decision expected in 2025, and that it anticipates additional global regulatory submissions. There are also product candidates in earlier stages of development for the treatment of ATTR amyloidosis with cardiomyopathy, including NTLA-2001 which is being developed by Intellia Therapeutics, Inc. and Regeneron and is in Phase 3 clinical development; NNC-6019 which is being developed by Novo Nordisk and is in Phase 2 clinical development; and NI006 which is being developed by Neurimmune AG and AstraZeneca plc and is in Phase 3 clinical development. We expect to face competition from any of these and potentially other additional new drugs that enter the market to treat patients with ATTR amyloidosis with cardiomyopathy.

ONPATTRO and AMVUTTRA are approved in certain jurisdictions for the treatment of certain patients with hATTR amyloidosis with polyneuropathy. We are aware of other approved products used to treat this disease, including WAINUA (eplontersen), a drug developed by Ionis in partnership with AstraZeneca plc, VYNDALAN/VYNDAMAX (tafamidis), and TEGSEDI (inotersen), which is developed and marketed by Ionis. There are also product candidates in various stages of clinical development for the treatment of hATTR amyloidosis patients with polyneuropathy. While we believe that ONPATTRO and AMVUTTRA have and will continue to have a competitive product profile for the treatment of patients with hATTR amyloidosis with polyneuropathy, it is possible that ONPATTRO and/or AMVUTTRA may not compete favorably with these products and product candidates, or others, and, as a result, may not achieve commercial success.

If we or our collaborators continue to successfully develop product candidates, and obtain approval for them, we and our collaborators will face competition based on many different factors, including:

- the safety and effectiveness of our or our collaborators' products relative to alternative therapies, if any;
- the ease with which our or our collaborators' products can be administered and the extent to which patients accept relatively new routes of administration;
- the timing and scope of regulatory approvals for these products;
- the availability and cost of manufacturing, marketing and sales capabilities;
- the price of our or our collaborators' products relative to alternative approved therapies;
- reimbursement coverage; and
- patent position.

We are aware of product candidates in various stages of clinical development for the treatment of PH1 which would compete with OXLUMO, our RNAi therapeutic approved in the U.S. and EU for the treatment of this disease, including Novo

Nordisk's product RIVFLOZA (nedosiran), which was approved for the treatment of PH1 in September 2023 and is expected to launch in 2024. RIVFLOZA is a once-monthly subcutaneous RNAi therapy that was developed by Dicerna. In April 2020, we and Dicerna granted each other a non-exclusive cross-license to our respective intellectual property related to lumasiran and Dicerna's nedosiran. In addition, several companies have investigational drugs in clinical development for the treatment of PH1, including BridgeBio, Chinook Therapeutics, Inc., and BioMarin Pharmaceutical, Inc.

Our competitors may develop or commercialize products with significant advantages over any products we or our collaborators develop based on any of the factors listed above or on other factors. In addition, our competitors may develop collaborations with or receive funding from larger pharmaceutical or biotechnology companies, providing them with an advantage over us and our collaborators. Our competitors may therefore be more successful in commercializing their products than we or our collaborators are, which could adversely affect our competitive position and business, prospects, operating results and financial condition. Competitive products may make any products we or our collaborators develop obsolete or noncompetitive before we can recover the expenses of developing and commercializing our product candidates. Such competitors could also recruit our employees, which could negatively impact our level of expertise and our ability to execute on our business plan. Furthermore, we and our collaborators also face competition from existing and new treatment methods that reduce or eliminate the need for drugs, such as the use of advanced medical devices. The development of new medical devices or other treatment methods for the diseases we and our collaborators are targeting could make our or our collaborators' product candidates noncompetitive, obsolete or uneconomical.

We and our collaborators face competition from other companies that are working to develop novel drugs and technology platforms using technology similar to ours, as well as from companies utilizing emerging technologies. If these companies develop drugs more rapidly than we or our collaborators do or their technologies, including delivery technologies, are more effective, our and our collaborators' ability to successfully commercialize our products may be adversely affected.

In addition to the competition we face from competing drugs in general, we and our collaborators also face competition from other companies working to develop novel drugs using technology that competes more directly with our own. We are aware of several other companies that are working to develop RNAi therapeutic products. Some of these companies are seeking, as we are, to develop chemically synthesized siRNAs as drugs. Others are following a gene therapy approach, with the goal of treating patients with synthetic, exogenously-introduced genes designed to produce siRNA-like molecules within cells. Companies working on chemically synthesized siRNAs include, but are not limited to, Arrowhead and its collaborators, Takeda Pharmaceutical Company Ltd., Janssen Pharmaceuticals, Inc., GlaxoSmithKline plc, and Amgen Inc.; Quark Pharmaceuticals, Inc.; Roche; Silence Therapeutics plc and its collaborators, AstraZeneca plc, Jiangsu Hansoh Pharmaceuticals Group Co., Ltd., and Mallinckrodt plc; Arbutus; Sylentis; and Novo Nordisk and its collaborators, Boehringer Ingelheim and Eli Lilly and Company. In addition, we granted licenses or options for licenses to Ionis, Benitec Biopharma Ltd., Arrowhead, Arbutus, Quark, Sylentis and other companies under which these companies may independently develop RNAi therapeutics against a limited number of targets. Any one of these companies may develop its RNAi technology more rapidly and more effectively than we do. In addition, as a result of agreements that we have entered into, Takeda has obtained a non-exclusive license, and Arrowhead, as the assignee of Novartis, has obtained specific exclusive licenses for 30 gene targets, that include access to certain aspects of our technology.

We and our collaborators also compete with companies working to develop antisense-based drugs. Similar to RNAi therapeutics, antisense drugs target mRNAs in order to suppress the activity of specific genes. Akcea Therapeutics, Inc., a wholly owned subsidiary of Ionis, has received marketing approval for an antisense drug, inotersen for the treatment of adult hATTR amyloidosis patients with stage 1 or stage 2 polyneuropathy. Several antisense drugs developed by Ionis have been approved and are currently marketed, and Ionis has multiple antisense product candidates in clinical trials. Ionis is also developing antisense drugs using ligand-conjugated GalNAc technology licensed from us, and these drugs have been shown to have increased potency at lower doses in clinical and pre-clinical studies, compared with antisense drugs that do not use such licensed GalNAc technology. The development of antisense drugs and antisense technology may become the preferred technology for drugs that target mRNAs to silence specific genes.

In addition to competition with respect to RNAi and with respect to specific products, we face substantial competition to discover and develop safe and effective means to deliver siRNAs to the relevant cell and tissue types. If our competitors develop safe and effective means to deliver siRNAs to the relevant cell and tissue types, our ability to successfully commercialize a competitive product would be adversely affected. In addition, third parties are expending substantial resources to discover and develop a safe and effective means of delivering siRNAs into the relevant cell and tissue types, including both private companies and academic laboratories. Some of our competitors have substantially greater resources than we do, and if our competitors negotiate exclusive access to delivery solutions developed by third parties, we may be unable to successfully commercialize our product candidates.

Risks Related to Our Common Stock

Our stock price has been and may in the future be volatile, and an investment in our common stock could suffer a decline in value.

Our stock price has been and may in the future be volatile. The stock market in general and the market for biotechnology companies in particular have experienced extreme price and volume volatility that has often been unrelated to the operating performance of particular companies. The market price of our common stock in the future could be significantly and adversely affected by many factors, including:

- the information contained in our quarterly earnings releases, including updates regarding our or our collaborators' commercialized products or product candidates, our net product and collaboration revenues and operating expenses for completed periods and financial guidance regarding future periods;
- the success of existing or new competitive products or technologies;
- regulatory actions with respect to our or our collaborators' products or product candidates;
- announcements by us or our competitors of significant acquisitions, collaborations, joint ventures, collaborations or capital commitments;
- the timing and results of clinical trials of our or our collaborators' other product candidates;
- commencement or termination of collaborations for our development programs;
- failure or discontinuation of any of our or our collaborators' development programs;
- results of clinical trials of our competitors' product candidates;
- regulatory or legal developments in the U.S. and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or clinical development programs;
- the results of our or our collaborators' efforts to develop additional product candidates or products;
- actual or anticipated changes in financial results or development timelines;
- announcement or expectation of additional financing efforts;
- sales of our common stock by us, our insiders or other stockholders;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in estimates or recommendations by any of the securities analysts that cover us;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions; and
- the other factors described in this "Risk Factors" section.

In the past, securities class action litigation has often been brought against companies following declines in the market price of their securities. This risk is especially relevant for biopharmaceutical companies, which have experienced significant stock price volatility in recent years. For example, in September 2019, we and certain of our current and former directors and officers, and the underwriters of our November 2017 stock offering were sued in a putative class action alleging violations of the federal securities laws. While this matter has been finally settled, we may be the target of additional litigation of this type in the future. Securities litigation against us could result in substantial costs and divert our management's attention and resources, which could cause serious harm to our business, prospects, operating results and financial condition. We maintain liability insurance; however, if any costs or expenses associated with litigation exceed our insurance coverage, we may be forced to bear some or all of these costs and expenses directly, which could be substantial. In addition, we have obligations to indemnify third parties, including our officers and directors and underwriters of our securities offerings, in connection with certain litigation, and those obligations may not be covered by insurance.

Sales of a substantial number of shares of our common stock, including by us, our officers or directors, or our significant stockholders, into the public market could cause the price of our common stock to decline.

A small number of our stockholders beneficially own a substantial amount of our common stock. As of March 31, 2024, our eight largest stockholders beneficially owned in excess of 50% of our outstanding shares of common stock. If we, our

officers or directors, or our significant stockholders sell substantial amounts of our common stock in the public market, or there is a perception that such sales may occur, the market price of our common stock could be adversely affected. Sales of common stock by our significant stockholders might make it more difficult for us to raise funds by selling equity or equity-related securities in the future at a time and price that we deem appropriate.

Anti-takeover provisions in our governing documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management or members of our board of directors.

Provisions in our certificate of incorporation and our bylaws may delay or prevent an acquisition of us or a change in the current members of our management or the members of our board of directors. Among other things, these provisions:

- establish a classified board of directors such that all members of our board of directors are not elected at one time;
- establish a prohibition on actions by our stockholders by written consent;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a “poison pill” that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors;
- allow the authorized number of our directors to be changed only by resolution of our board of directors.
- limit who may call a special meetings of stockholders;
- require the approval of the holders of at least 75% of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our charter or bylaws;
- limit the manner in which stockholders can remove directors from our board of directors; and
- establish advance notice requirements for election to our board of directors and for proposing matters that can be acted upon at stockholder meetings.

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner. These provisions would apply even if the proposed merger or acquisition could be considered beneficial by some stockholders.

We expect that results from our and our collaborators’ clinical development activities and the clinical development activities of our competitors will continue to be released periodically and may result in significant volatility in the price of our common stock.

Any new information regarding our and our collaborators’ products and product candidates or competitive products or potentially competitive product candidates can substantially affect investors’ perceptions regarding our future prospects. We, our collaborators, and our competitors periodically provide updates regarding drug development programs, typically through press releases, conference calls and presentations at medical conferences. These periodic updates often include interim or final results from clinical trials conducted by us or our competitors and/or information about our or our competitors’ expectations regarding regulatory filings and submissions as well as future clinical development of our products or product candidates, competitive products or potentially competitive product candidates. The timing of the release of information by us regarding our drug development programs is often beyond our control and is influenced by the timing of receipt of data from our clinical trials and by the general preference among pharmaceutical companies to disclose clinical data during medical conferences. In addition, the information disclosed about our clinical trials, or our competitors’ clinical trials, may be based on interim rather than final data that may involve interpretation difficulties and may in any event not accurately predict final results. The release of such information may result in volatility in the price of our common stock. For example, in late 2021 our stock price was negatively impacted following BridgeBio’s public disclosure of the results of Part A of the Phase 3 clinical trial of acoramidis for the treatment of ATTR amyloidosis with cardiomyopathy.

Risks Related to Our Convertible Notes

We may not have sufficient cash flow from our business to pay our indebtedness.

As of March 31, 2024, we had \$1.02 billion in aggregate principal amount of Notes outstanding. The interest rate for the Notes is fixed at 1.00% per annum and is payable semi-annually in arrears on May 15 and September 15 of each year, beginning on March 15, 2023. Our ability to make scheduled payments of the principal of, to pay interest on or to refinance our indebtedness, including the Notes, or to make cash payments in connection with any conversions of Notes, depends on our future performance, which is subject to economic, financial, competitive and other factors beyond our control. Our business may not generate cash flow from operations in the future sufficient to service our debt and make necessary capital expenditures. If we are unable to generate such cash flow, we may be required to adopt one or more alternatives, such as selling assets, restructuring debt or obtaining additional debt financing or equity capital on terms that may be onerous or highly dilutive. Our

ability to refinance any future indebtedness will depend on the capital markets and our financial condition at such time. We may not be able to engage in any of these activities or engage in these activities on desirable terms, which could result in a default on our debt obligations.

In addition, our indebtedness, combined with our other financial obligations and contractual commitments, could have other important consequences. For example, it could:

- make us more vulnerable to adverse changes in general U.S. and worldwide economic, industry and competitive conditions and adverse changes in government regulation;
- limit our flexibility in planning for, or reacting to, changes in our business and our industry;
- place us at a disadvantage compared to our competitors who have less debt;
- limit our ability to borrow additional amounts to fund acquisitions, for working capital and for other general corporate purposes; and
- make an acquisition of our company less attractive or more difficult.

Any of these factors could harm our business, prospects, operating results and financial condition. In addition, if we incur additional indebtedness, the risks related to our business and our ability to service or repay our indebtedness would increase.

We may not have the ability to raise the funds necessary to settle for cash conversions of the Notes or to repurchase the Notes for cash upon a fundamental change.

Holders of the Notes have the right to require us to repurchase their Notes upon the occurrence of a fundamental change (as defined in the indenture governing the Notes) at a repurchase price equal to 100% of the principal amount of the Notes to be repurchased, plus accrued and unpaid interest, if any. Upon conversion of the Notes, unless we elect to deliver solely shares of our common stock to settle such conversion (other than paying cash in lieu of delivering any fractional share), we will be required to make cash payments in respect of the Notes being converted. We may not have enough available cash or be able to obtain financing at the time we are required to make repurchases of Notes surrendered or Notes being converted. In addition, our ability to repurchase the Notes or to pay cash upon conversions of the Notes may be limited by law, by regulatory authority or by agreements governing our future indebtedness. Our failure to repurchase Notes at a time when the repurchase is required by the indenture governing such notes or to pay any cash payable on future conversions of the Notes as required by such indenture would constitute a default under such indenture. A default under the indenture governing the Notes or the fundamental change itself could also lead to a default under agreements governing our future indebtedness. If the repayment of the related indebtedness were to be accelerated after any applicable notice or grace periods, we may not have sufficient funds to repay the indebtedness and repurchase the Notes or make cash payments upon conversions.

The conditional conversion feature of the Notes, if triggered, may adversely affect our liquidity.

In the event the conditional conversion feature of the Notes is triggered, holders of the Notes will be entitled to convert the Notes at any time during specified periods at their option. If one or more holders elect to convert their Notes, unless we elect to satisfy our conversion obligation by delivering solely shares of our common stock (other than paying cash in lieu of delivering any fractional share), we would be required to settle a portion or all of our conversion obligation through the payment of cash, which could adversely affect our liquidity. In addition, even if holders do not elect to convert their Notes, we could be required under applicable accounting rules to reclassify all or a portion of the outstanding principal of the Notes as a current liability, rather than long-term liability, which would result in a material reduction of our net working capital.

Transactions relating to the Notes may affect the value of our common stock.

The conversion of some or all of the Notes would dilute the ownership interests of existing stockholders to the extent we satisfy our conversion obligation by delivering shares of our common stock upon any conversion of such Notes. The Notes may become in the future convertible at the option of their holders under certain circumstances. If holders of the Notes elect to convert their notes, we may settle our conversion obligation by delivering to them a significant number of shares of our common stock, which would cause dilution to our existing stockholders.

In addition, in connection with the issuance of the Notes, we entered into the Capped Calls with certain financial institutions, or the Option Counterparties. The Capped Calls are generally expected to reduce potential dilution to our common stock upon any conversion or settlement of the Notes and/or offset any cash payments we are required to make in excess of the principal amount of converted Notes, with such reduction and/or offset subject to a cap.

In connection with establishing their initial hedges of the Capped Calls, the Option Counterparties or their respective affiliates entered into various derivative transactions with respect to our common stock and/or purchased shares of our common stock concurrently with or shortly after the pricing of the Notes.

From time to time, the Option Counterparties or their respective affiliates may modify their hedge positions by entering into or unwinding various derivative transactions with respect to our common stock and/or purchasing or selling our common stock or other securities of ours in secondary market transactions prior to the maturity of the Notes (and are likely to do so

following any conversion of the Notes, any repurchase of the Notes by us on any fundamental change repurchase date, any redemption date, or any other date on which the Notes are retired by us, in each case, if we exercise our option to terminate the relevant portion of the Capped Calls). This activity could cause a decrease and/or increased volatility in the market price of our common stock.

We do not make any representation or prediction as to the direction or magnitude of any potential effect that the transactions described above may have on the price of the Notes or our common stock. In addition, we do not make any representation that the Option Counterparties will engage in these transactions or that these transactions, once commenced, will not be discontinued without notice.

We are subject to counterparty risk with respect to the Capped Calls.

The Option Counterparties are financial institutions, and we will be subject to the risk that any or all of them might default under the Capped Calls. Our exposure to the credit risk of the Option Counterparties will not be secured by any collateral. Past global economic conditions have resulted in the actual or perceived failure or financial difficulties of many financial institutions. If an Option Counterparty becomes subject to insolvency proceedings, we will become an unsecured creditor in those proceedings with a claim equal to our exposure at that time under the Capped Calls with such Option Counterparty. Our exposure will depend on many factors but, generally, an increase in our exposure will be correlated to an increase in the market price and in the volatility of our common stock. In addition, upon a default by an Option Counterparty, we may suffer adverse tax consequences and more dilution than we currently anticipate with respect to our common stock. We can provide no assurances as to the financial stability or viability of the Option Counterparties.

The accounting method for convertible debt securities that may be settled in cash, such as the Notes, could have a material effect on our reported financial results.

The accounting method for reflecting the Notes on our condensed consolidated balance sheet, accruing interest expense for the Notes and reflecting the underlying shares of our common stock in our reported diluted earnings per share may adversely affect our reported earnings and financial condition.

In August 2020, the Financial Accounting Standards Board published an Accounting Standards Update, which we refer to as ASU 2020-06, which simplified certain of the accounting standards that apply to convertible notes. ASU 2020-06 became effective for us beginning January 1, 2022.

In accordance with ASU 2020-06, the Notes are reflected as a liability on our condensed consolidated balance sheets, with the initial carrying amount equal to the principal amount of the Notes, net of issuance costs. The issuance costs were treated as a debt discount for accounting purposes, which is being amortized into interest expense over the term of the Notes. As a result of this amortization, the interest expense that we expect to recognize for the Notes for accounting purposes will be greater than the cash interest payments we will pay on the Notes, which will result in lower reported net income or higher reported net loss, as the case may be.

In addition, the shares of common stock underlying the Notes are reflected in our diluted earnings per share using the “if converted” method, in accordance with ASU 2020-06. Under this method, diluted earnings per share is generally calculated assuming that all the Notes were converted solely into shares of common stock at the beginning of the reporting period, unless the result would be anti-dilutive. The application of the if-converted method may reduce our reported diluted earnings per share to the extent we are profitable in the future, and accounting standards may change in the future in a manner that may adversely affect our diluted earnings per share.

Furthermore, if any of the conditions to the convertibility of the Notes is satisfied, then we may be required under applicable accounting standards to reclassify the liability carrying value of the Notes as a current, rather than a long-term, liability. This reclassification could be required even if no holders actually convert their Notes and could materially reduce our reported working capital.

ITEM 5. OTHER INFORMATION

Adoption of 10b5-1 Trading Plans by Our Officers and Directors

During our fiscal quarter ended March 31, 2024, certain of our officers (as defined in Rule 16a-1(f) under the Exchange Act) and directors entered into contracts, instructions or written plans for the purchase or sale of our securities that are intended to satisfy the conditions specified in Rule 10b5-1(c) under the Exchange Act for an affirmative defense against liability for trading in securities on the basis of material nonpublic information. We refer to these contracts, instructions, and written plans as “Rule 10b5-1 trading plans” and each one as a “Rule 10b5-1 trading plan.” We describe the material terms of these Rule 10b5-1 trading plans below.

Yvonne L. Greenstreet, MBChB, MBA, Chief Executive Officer and Director

On March 12, 2024, Yvonne L. Greenstreet, MBChB, MBA, our Chief Executive Officer, entered into a Rule 10b5-1 trading plan that provides that Dr. Greenstreet, acting through a broker, may sell up to an aggregate of 37,241 shares of our

common stock received upon the settlement of awards granted to Dr. Greenstreet as equity incentive compensation, subject to adjustments for stock splits, stock combinations, stock dividends and other similar changes to our common stock. Sales of shares under the plan may only occur if the market price of our common stock is above specified prices from June 19, 2024 to March 7, 2025. The plan is scheduled to terminate on March 7, 2025, subject to earlier termination upon the sale of all shares subject to the plan, upon termination by Dr. Greenstreet or the broker, or as otherwise provided in the plan.

Amy W. Schulman, Director

On February 28, 2024, Amy W. Schulman, Chair of our board of directors, entered into a Rule 10b5-1 trading plan that provides that Ms. Schulman, acting through a broker, may sell up to an aggregate of 30,200 shares of our common stock received upon the exercise of options granted to Ms. Schulman as director compensation, subject to adjustments for stock splits, stock combinations, stock dividends and other similar changes to our common stock. Sales of shares under the plan may only occur if the market price of our common stock is above specified prices from May 29, 2024 to November 15, 2024. The plan is scheduled to terminate on November 15, 2024, subject to earlier termination upon the sale of all shares subject to the plan upon termination by Ms. Schulman or the broker, or as otherwise provided in the plan.

ITEM 6. EXHIBITS

10.1#†	Amendment No. 2 entered into as of March 7, 2024 to the Master Collaboration Agreement dated as of April 8, 2019 by and between the Registrant and Regeneron Pharmaceuticals, Inc.
31.1#	Certification of principal executive officer pursuant to Rule 13a-14(a) promulgated under the Securities Exchange Act of 1934, as amended
31.2#	Certification of principal financial officer pursuant to Rule 13a-14(a) promulgated under the Securities Exchange Act of 1934, as amended
32.1#+	Certification of principal executive officer pursuant to Rule 13a-14(b) promulgated under the Securities Exchange Act of 1934, as amended, and Section 1350 of Chapter 63 of Title 18 of the United States Code
32.2#+	Certification of principal financial officer pursuant to Rule 13a-14(b) promulgated under the Securities Exchange Act of 1934, as amended, and Section 1350 of Chapter 63 of Title 18 of the United States Code
101.SCH	Inline XBRL Taxonomy Extension Schema Document
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document
104	Cover Page Interactive Data File (formatted as inline XBRL with applicable taxonomy extension information contained in Exhibits 101.*)
#	Filed herewith.
†	Portions of this exhibit (indicated by asterisks) have been omitted in accordance with the rules of the Securities and Exchange Commission because such information (i) is not material and (ii) would likely cause competitive harm to the Registrant if publicly disclosed.
+	This certification will not be deemed “filed” for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or the Exchange Act, or otherwise subject to the liability of that section. Such certification will not be deemed to be incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Exchange Act, except to the extent specifically incorporated by reference into such filing.

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.

ALNYLAM PHARMACEUTICALS, INC.

Date: May 2, 2024

/s/ Yvonne L. Greenstreet, MBChB, MBA

Yvonne L. Greenstreet, MBChB, MBA
Chief Executive Officer
(Principal Executive Officer)

Date: May 2, 2024

/s/ Jeffrey V. Poulton

Jeffrey V. Poulton
Executive Vice President, Chief Financial Officer
(Principal Financial and Accounting Officer)

CERTAIN INFORMATION IN THIS DOCUMENT, MARKED BY [**], HAS BEEN EXCLUDED PURSUANT TO REGULATION S-K, ITEM 601(b)(10)(iv). SUCH EXCLUDED INFORMATION IS NOT MATERIAL AND IS THE TYPE THAT THE REGISTRANT TREATS AS PRIVATE OR CONFIDENTIAL.

**Amendment No. 2
to the Master Agreement**

This Amendment No. 2 (“**Amendment No. 2**”) to the Master Agreement is entered into and effective as of March 7, 2024 (“**Amendment No. 2 Effective Date**”) by and between Regeneron Pharmaceuticals, Inc., a corporation organized under the laws of New York (“**Regeneron**”), and Alnylam Pharmaceuticals, Inc., a corporation organized under the laws of Delaware (“**Alnylam**”). All capitalized terms not otherwise defined herein shall have the meanings ascribed to such terms in the Agreement.

Recitals

WHEREAS, Regeneron and Alnylam are parties to that certain Master Agreement dated April 8, 2019 (“**Master Agreement**”) as amended by Amendment No. 1 to the Master Agreement dated April 10, 2023 (“**Amendment No. 1**”) (the Master Agreement, together with Amendment No. 1, the “**Agreement**”);

WHEREAS, pursuant to Amendment No. 1, Regeneron and Alnylam agreed to conduct certain technology development activities related to the generation and evaluation of [**], in accordance with the [**] Research Plan attached to the Agreement as Schedule 1.277;

WHEREAS, the Parties now wish to further amend the Agreement and the [**] Research Plan as provided herein.

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

1. The Parties hereby agree that the [**] Research Plan attached to the Agreement as Schedule 1.277 pursuant to Amendment No. 1 is hereby amended by adding the research activities attached hereto as Appendix A to Schedule 1.277.
2. Section 3.2.3(f)(i) is hereby restated and amended, effective as of the Effective Date of the Agreement, as follows:

(i) The Parties agree to conduct certain technology development activities related to the generation and evaluation of [**], in accordance with the mutually agreed research plan attached hereto as Schedule 1.277 (the “[**] **Research Plan**”). Each Party will provide [**] updates on such Party’s Technology Development Activities under the [**] Research Plan to the JSC. The [**] Research Plan may be updated or amended by mutual written agreement of the Parties (via

the JSC and reflected in the JSC meeting minutes) from time to time. In the event of any dispute between the Parties related to an update or amendment to the [**] Research Plan, then such dispute will be deemed to be a Deadlocked Dispute and resolved in accordance with Section 2.2.3(a)(ii). Under the [**] Research Plan, Regeneron will provide [**] antibody ligands and Alnylam will provide siRNAs for the activities under the workplan.

3. Except as specifically amended herein, all other terms of the Agreement shall remain in full force and effect. The Parties may execute this Amendment No. 2 in counterparts, each of which is deemed an original, but all of which together constitute one and the same agreement. This Amendment No. 2 may be executed or delivered electronically or by facsimile transmission, and the Parties hereby agree that any electronic or facsimile signatures hereto are legal, valid and enforceable as originals.

[signatures follow]

THIS AMENDMENT NO. 2 IS EXECUTED by the authorized representatives of the Parties as of the Amendment No. 2 Effective Date.

**ALNYLAM PHARMACEUTICALS, INC. REGENERON PHARMACEUTICALS,
INC.**

By: /s/ Jeff Poulton

By: /s/ Kerry Reinertsen

Name: Jeff Poulton

Name: Kerry Reinertsen

Title: Chief Financial Officer

Title: SVP Strategic Alliances

Appendix A
Additional Research Activities for [] Research Plan**

[**]

CERTIFICATION

I, Yvonne L. Greenstreet, MBChB, certify that:

- 1) I have reviewed this Quarterly Report on Form 10-Q of Alnylam 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 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 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.

Dated: May 2, 2024

/s/ Yvonne L. Greenstreet, MBChB, MBA

Yvonne L. Greenstreet, MBChB, MBA
Chief Executive Officer

CERTIFICATION

I, Jeffrey V. Poulton, certify that:

- 1) I have reviewed this Quarterly Report on Form 10-Q of Alnylam 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 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 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.

Dated: May 2, 2024

/s/ Jeffrey V. Poulton

Jeffrey V. Poulton
Executive Vice President, Chief Financial Officer

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

In connection with the Quarterly Report on Form 10-Q of Alnylam Pharmaceuticals, Inc. (the "Company") for the quarter ended March 31, 2024 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Yvonne L. Greenstreet, MBChB, Chief Executive Officer of the Company, hereby certifies, pursuant to Section 1350 of Chapter 63 of Title 18, United States Code, that to his knowledge:

- (1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and
- (2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: May 2, 2024

/s/ Yvonne L. Greenstreet, MBChB, MBA

Yvonne L. Greenstreet, MBChB, MBA
Chief Executive Officer

A signed original of this written statement required by Section 906 has been provided to the Company and will be retained by the Company and furnished to the Securities and Exchange Commission or its staff upon request.

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

In connection with the Quarterly Report on Form 10-Q of Alnylam Pharmaceuticals, Inc. (the "Company") for the quarter ended March 31, 2024 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Jeffrey V. Poulton, Executive Vice President, Chief Financial Officer, hereby certifies, pursuant to Section 1350 of Chapter 63 of Title 18, United States Code, that to his knowledge:

- (1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and
- (2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: May 2, 2024

/s/ Jeffrey V. Poulton

Jeffrey V. Poulton
Executive Vice President, Chief Financial Officer

A signed original of this written statement required by Section 906 has been provided to the Company and will be retained by the Company and furnished to the Securities and Exchange Commission or its staff upon request.