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 June 30, 2023

OR

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

For the transition period from _____ to _____

Commission File Number 001-36407

ALNYLAM PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware **(State or Other Jurisdiction of Incorporation or Organization)**	**77-0602661** **(I.R.S. Employer Identification No.)**
675 West Kendall Street, Henri A. Termeer Square Cambridge, MA **(Address of Principal Executive Offices)**	**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 x No ☐

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

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

Large accelerated filer	x	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 x

At July 28, 2023, the registrant had 125,000,652 shares of Common Stock, $0.01 par value per share, outstanding.

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

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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 partner's plans with respect to Leqvio;
- our future ability to successfully expand the indications for ONPATTRO and AMVUTTRA;
- 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 partners' 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 and GEMINI platforms 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;
- risks related to the direct or indirect impact of the novel coronavirus, or COVID-19, global pandemic, emerging or future variants of COVID-19 or any future pandemic, or public health emergency, 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 ongoing conflict in Ukraine, including disruptions to our clinical 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 partners), by our or their contract manufacturers or by us or our partners;
- our progress continuing to build and leverage our 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 partners', 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 *Alnylam P*^{5}*x25* 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;
- 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 and to successfully execute on our *Alnylam P^{5}x25* strategy;
- 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;
- our expectations regarding the effect of the capped call transactions and the anticipated market activities of the option counterparties and/or their respective affiliates; and
- other risks and uncertainties, including those listed under the caption Part II, Item 1A, "Risk Factors" of this Quarterly Report on Form 10-Q.

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 SEC.

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

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

	June 30, 2023	December 31, 2022
ASSETS		
Current assets:		
Cash and cash equivalents	$ 657,800	$ 866,394
Marketable debt securities	1,372,451	1,297,890
Marketable equity securities	27,256	28,122
Accounts receivable, net	220,635	237,963
Inventory	100,453	128,962
Prepaid expenses and other current assets	145,452	132,916
Total current assets	2,524,047	2,692,247
Property, plant and equipment, net	527,474	523,494
Operating lease right-of-use assets	208,801	215,136
Restricted investments	49,388	49,390
Other assets	92,686	66,092
Total assets	$ 3,402,396	$ 3,546,359
LIABILITIES AND STOCKHOLDERS' DEFICIT		
Current liabilities:		
Accounts payable	$ 59,746	$ 98,094
Accrued expenses	598,530	545,460
Operating lease liability	42,074	41,967
Deferred revenue	54,639	42,105
Liability related to the sale of future royalties	33,650	40,289
Total current liabilities	788,639	767,915
Operating lease liability, net of current portion	253,416	261,339
Deferred revenue, net of current portion	194,129	193,791
Convertible debt	1,018,843	1,016,942
Liability related to the sale of future royalties, net of current portion	1,298,446	1,252,015
Other liabilities	257,054	212,580
Total liabilities	3,810,527	3,704,582
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 June 30, 2023 and December 31, 2022	—	—
Common stock, $0.01 par value per share, 250,000 shares authorized; 124,901 shares issued and outstanding as of June 30, 2023; 123,925 shares issued and outstanding as of December 31, 2022	1,250	1,240
Additional paid-in capital	6,647,173	6,454,540
Accumulated other comprehensive loss	(37,080)	(44,654)
Accumulated deficit	(7,019,474)	(6,569,349)
Total stockholders' deficit	(408,131)	(158,223)
Total liabilities and stockholders' deficit	$ 3,402,396	$ 3,546,359

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 June 30,		Six Months Ended June 30,	
	2023	2022	2023	2022
Statements of Operations				
Revenues:				
Net product revenues	$ 305,705	$ 213,515	$ 582,033	$ 400,387
Net revenues from collaborations	5,844	9,025	42,306	34,970
Royalty revenue	7,205	2,278	13,705	2,720
Total revenues	318,754	224,818	638,044	438,077
Operating costs and expenses:				
Cost of goods sold	75,336	34,038	116,768	57,495
Cost of collaborations and royalties	10,034	6,770	23,471	18,940
Research and development	248,526	205,712	479,095	375,605
Selling, general and administrative	214,689	169,984	398,348	324,455
Total operating costs and expenses	548,585	416,504	1,017,682	776,495
Loss from operations	(229,831)	(191,686)	(379,638)	(338,418)
Other (expense) income:				
Interest expense	(30,035)	(42,609)	(58,990)	(84,971)
Interest income	21,075	1,899	39,730	2,911
Other expense, net	(35,418)	(42,277)	(47,673)	(93,551)
Total other expense, net	(44,378)	(82,987)	(66,933)	(175,611)
Loss before income taxes	(274,209)	(274,673)	(446,571)	(514,029)
Provision for income taxes	(1,815)	(2,729)	(3,554)	(3,714)
Net loss	$ (276,024)	$ (277,402)	$ (450,125)	$ (517,743)
Net loss per common share - basic and diluted	$ (2.21)	$ (2.29)	$ (3.62)	$ (4.29)
Weighted-average common shares used to compute basic and diluted net loss per common share	124,659	120,896	124,387	120,646
Statements of Comprehensive Loss				
Net loss	$ (276,024)	$ (277,402)	$ (450,125)	$ (517,743)
Other comprehensive income (loss):				
Unrealized (loss) gain on marketable securities	(2,025)	(1,734)	2,100	(8,951)
Foreign currency translation gain (loss)	4,073	(2,459)	5,483	(83)
Defined benefit pension plans, net of tax	(4)	34	(9)	69
Total other comprehensive income (loss)	2,044	(4,159)	7,574	(8,965)
Comprehensive loss	$ (273,980)	$ (281,561)	$ (442,551)	$ (526,708)

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

ALNYLAM PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF STOCKHOLDERS' (DEFICIT) EQUITY
(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, 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 expense	—	—	41,136	—	—	41,136
Other comprehensive income	—	—	—	5,530	—	5,530
Net loss	—	—	—	—	(174,101)	(174,101)
Balance as of March 31, 2023	124,241	1,243	6,522,091	(39,124)	(6,743,450)	(259,240)
Exercise of common stock options, net of tax withholdings	372	4	38,111	—	—	38,115
Issuance of common stock under equity plans	288	3	9,981	—	—	9,984
Stock-based compensation expense	—	—	76,990	—	—	76,990
Other comprehensive income	—	—	—	2,044	—	2,044
Net loss	—	—	—	—	(276,024)	(276,024)
Balance as of June 30, 2023	124,901	$ 1,250	$ 6,647,173	$ (37,080)	$ (7,019,474)	$ (408,131)

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

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

	Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balance as of December 31, 2021	120,182	$ 1,202	$ 6,058,453	$ (33,259)	$ (5,438,193)	$ 588,203
Exercise of common stock options, net of tax withholdings	524	5	28,054	—	—	28,059
Issuance of common stock under equity plans	23	—	—	—	—	—
Stock-based compensation expense	—	—	30,051	—	—	30,051
Other comprehensive loss	—	—	—	(4,806)	—	(4,806)
Net loss	—	—	—	—	(240,341)	(240,341)
Balance as of March 31, 2022	120,729	1,207	6,116,558	(38,065)	(5,678,534)	401,166
Exercise of common stock options, net of tax withholdings	192	2	13,890	—	—	13,892
Issuance of common stock under equity plans	71	1	8,089	—	—	8,090
Stock-based compensation expense	—	—	34,453	—	—	34,453
Other comprehensive loss	—	—	—	(4,159)	—	(4,159)
Net loss	—	—	—	—	(277,402)	(277,402)
Balance as of June 30, 2022	120,992	$ 1,210	$ 6,172,990	$ (42,224)	$ (5,955,936)	$ 176,040

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)

	Six Months Ended June 30,	
	2023	**2022**
Cash flows from operating activities:		
Net loss	$ (450,125)	$ (517,743)
Non-cash adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	27,244	19,557
Amortization and interest accretion related to operating leases	22,282	20,458
Non-cash interest expense on liability related to the sale of future royalties	51,647	54,704
Stock-based compensation	115,749	59,764
Realized and unrealized loss on marketable equity securities	867	32,258
Change in fair value of development derivative liability	36,686	45,692
Other	(8,252)	17,830
Changes in operating assets and liabilities:		
Accounts receivable, net	16,183	46,095
Inventory	1,582	(7,274)
Prepaid expenses and other assets	(29,109)	(51,159)
Accounts payable, accrued expenses and other liabilities	766	19,407
Operating lease liability	(23,847)	(21,434)
Deferred revenue	12,866	(12,167)
Net cash used in operating activities	(225,461)	(294,012)
Cash flows from investing activities:		
Purchases of property, plant and equipment	(29,810)	(33,914)
Purchases of marketable securities	(812,887)	(1,096,275)
Sales and maturities of marketable securities	757,767	1,134,138
Proceeds from maturity of restricted investments	58,475	24,225
Purchases of restricted investments	(58,475)	(32,725)
Other investing activities	—	(75)
Net cash used in investing activities	(84,930)	(4,626)
Cash flows from financing activities:		
Proceeds from exercise of stock options and other types of equity, net	91,765	49,626
Proceeds from development derivative	8,000	15,667
Net cash provided by financing activities	99,765	65,293
Effect of exchange rate changes on cash, cash equivalents and restricted cash	2,046	(11,073)
Net decrease in cash, cash equivalents and restricted cash	(208,580)	(244,418)
Cash, cash equivalents and restricted cash, beginning of period	868,556	822,153
Cash, cash equivalents and restricted cash, end of period	$ 659,976	$ 577,735
Supplemental disclosure of cash flows:		
Cash paid for interest	$ 17,128	$ 29,060
Supplemental disclosure of noncash investing activities:		
Capital expenditures included in accounts payable and accrued expenses	$ 5,663	$ 6,518

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, 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 alliances 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 partners. We have devoted substantially all of our efforts to business planning, research, development, manufacturing and early commercial efforts, acquiring, filing and expanding intellectual property rights, recruiting management and technical staff, and raising capital.

In early 2021, we launched our *Alnylam P^{5}x25* strategy, which focuses on our planned transition to a top-tier biotech company by the end of 2025. With *Alnylam P^{5}x25*, 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 June 30, 2023, we have five marketed products, including one partnered 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., Europe and Japan.

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, 2022, which were included in our Annual Report on Form 10-K that was filed with the Securities and Exchange Commission on February 23, 2023. 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, 2022.

Use of Estimates

The preparation of financial statements in conformity with accounting principles generally accepted in the United States of America, or 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, 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 June 30, 2023, together with the cash we expect to generate from product sales and under our current alliances, will be sufficient to enable us to advance our *Alnylam P^{5}x25* strategy for at least the next 12 months from the filing of this Quarterly Report on Form 10-Q.

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

3. NET PRODUCT REVENUES

Net product revenues consist of the following:

(In thousands)	Three Months Ended June 30, 2023	Three Months Ended June 30, 2022	Six Months Ended June 30, 2023	Six Months Ended June 30, 2022
ONPATTRO				
United States	$ 25,560	$ 71,085	$ 55,377	$ 133,392
Europe	56,393	56,787	116,071	109,968
Rest of World	9,505	25,556	22,503	47,077
Total	91,458	153,428	193,951	290,437
AMVUTTRA				
United States	96,469	—	175,482	—
Europe	14,405	—	21,173	—
Rest of World	21,262	—	37,249	—
Total	132,136	—	233,904	—
GIVLAARI				
United States	35,196	29,661	65,487	53,336
Europe	14,051	13,894	28,522	23,582
Rest of World	8,652	1,595	11,796	3,509
Total	57,899	45,150	105,805	80,427
OXLUMO				
United States	8,794	7,121	17,851	12,533
Europe	12,216	7,593	25,525	15,751
Rest of World	3,202	223	4,997	1,239
Total	24,212	14,937	48,373	29,523
Total net product revenues	$ 305,705	$ 213,515	$ 582,033	$ 400,387

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

(In thousands)	As of June 30, 2023	As of December 31, 2022
Receivables included in “Accounts receivable, net”	$ 184,158	$ 203,844

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 June 30,		Six Months Ended June 30,	
	2023	2022	2023	2022
Regeneron Pharmaceuticals	$ (2,837)	$ 14	$ 17,153	$ 12,426
Novartis AG	8,627	8,533	23,560	21,669
Other	54	478	1,593	875
Total	$ 5,844	$ 9,025	$ 42,306	$ 34,970

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

(In thousands)	As of June 30, 2023	As of December 31, 2022
Receivables included in “Accounts receivable, net”	$ 28,135	$ 32,342
Contract liabilities included in “Deferred revenue”	$ 248,603	$ 235,528

We recognized revenue of $4.8 million and $10.3 million in the three and six months ended June 30, 2023, respectively, and revenue of $5.3 million in the six months ended June 30, 2022, that was included in the contract liability balance at the beginning of the period. Revenue recognized from amounts included in the contract liability balance at the beginning of the period was immaterial for the three months ended June 30, 2022.

In order 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 collaboration partner:

	Three Months Ended June 30,					
	2023			2022		
(In thousands)	Clinical Trial and Manufacturing	External Services	Other	Clinical Trial and Manufacturing	External Services	Other
Regeneron Pharmaceuticals	$ 9,956	$ 910	$ 9,330	$ 1,677	$ 365	$ 9,645
Other	85	58	405	—	280	177
Total	$ 10,041	$ 968	$ 9,735	$ 1,677	$ 645	$ 9,822

	Six Months Ended June 30,					
	2023			2022		
(In thousands)	Clinical Trial and Manufacturing	External Services	Other	Clinical Trial and Manufacturing	External Services	Other
Regeneron Pharmaceuticals	$ 18,472	$ 2,150	$ 18,693	$ 3,114	$ 987	$ 18,953
Other	397	184	765	156	322	337
Total	$ 18,869	$ 2,334	$ 19,458	$ 3,270	$ 1,309	$ 19,290

The research and development expenses incurred for the agreements included in the table above consist of costs incurred for (i) clinical expenses, including manufacturing of clinical 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 and six months ended June 30, 2023 and 2022, we did not incur material selling, general and administrative expenses related to our collaboration agreements.

In addition, we recognized a reduction to our research and development expenses of $4.5 million and $10.2 million for the three and six months ended June 30, 2023, respectively, and $3.5 million and $7.4 million for the three and six months ended June 30, 2022, respectively, from cost reimbursement due under certain of our collaboration agreements with Regeneron Pharmaceuticals, Inc., or Regeneron, accounted for under Accounting Standards Codification, or ASC, Topic 808, Collaborative Arrangements, or ASC 808.

Product Alliances

Regeneron Pharmaceuticals, Inc.

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 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, which became effective on May 21, 2019. In connection with the Regeneron Master Agreement, we and Regeneron entered into (i) a binding co-co collaboration term sheet covering the continued development of cemdisiran, our C5 small interfering RNA, or siRNA, currently in Phase 2 development for C5 complement-mediated diseases, as a monotherapy and (ii) a binding license term sheet to evaluate anti-C5 antibody-siRNA combinations for C5 complement-mediated diseases including evaluating the combination of Regeneron's pozelimab (REGN3918), currently in Phase 3 development, and cemdisiran. The C5 co-co collaboration and license agreements were executed in August 2019.

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 Master Agreement have been combined for accounting purposes and treated as a single agreement.

In connection with the Regeneron Master Agreement, Regeneron made an upfront payment of $400.0 million. We are also eligible to receive up to an additional $200.0 million in milestone payments upon achievement of certain criteria during early clinical development for eye and CNS programs. 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 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.

The research license is 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 that is not available in the marketplace. Similarly, the worldwide license to cemdisiran for combination therapies is 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 cemdisiran monotherapy 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.

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 will be 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 future milestones upon the achievement of certain criteria during early clinical development for the eye and CNS programs. 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:

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

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 June 30, 2023, the total transaction price was determined to be $549.3 million, a decrease of $9.6 million from December 31, 2022. As of June 30, 2023, 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.

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, in thousands:

	Transaction Price Allocated	Deferred Revenue	
Performance Obligations	As of June 30, 2023	As of June 30, 2023	As of December 31, 2022
Research Services Obligation	$ 205,680	$ 45,000	$ 26,200
C5 License Obligation	97,600	3,800	7,000
C5 Co-Co Obligation	246,000	189,400	193,600
	$ 549,280	$ 238,200	$ 226,800

	Revenue Recognized During			
	Three Months Ended June 30,		Six Months Ended June 30,	
Performance Obligations	2023	2022	2023	2022
Research Services Obligation	$ (17,000)	$ 1,600	$ (6,300)	$ 8,800
C5 License Obligation	3,100	(4,800)	5,300	(3,500)
C5 Co-Co Obligation	1,700	1,700	4,200	4,000
	$ (12,200)	$ (1,500)	$ 3,200	$ 9,300

As of June 30, 2023, 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 $276.3 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, or PCSK9, 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 rights and obligations under the MDCO License Agreement. Additional details regarding the terms, milestones earned upon the achievement of certain events and additional milestones we are entitled to receive upon the achievement of future events under the MDCO License Agreement are described in Note 4 of the Notes to Consolidated Financial Statements included in our Annual Report on Form 10-K for the year ended December 31, 2022, as filed with the Securities and Exchange Commission on February 23, 2023.

Novartis License Agreement

In December 2021, we and Novartis entered into a collaboration and license agreement, or the Novartis License Agreement, pursuant to which we granted to Novartis an exclusive, worldwide license to develop, manufacture and commercialize siRNAs targeting end-stage liver disease, or ESLD, potentially leading to the development of a treatment designed to promote the regrowth of functional liver cells and to provide an alternative to transplantation for patients with liver failure. Additional details regarding the terms and transaction price under the Novartis License Agreement are described in Note 4 of the Notes to Consolidated Financial Statements included in our Annual Report on Form 10-K for the year ended December 31, 2022, as filed with the Securities and Exchange Commission on February 23, 2023.

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.

5. 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 50% of royalties payable, or Royalty Interest, 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 55% of the Royalty Interest beginning on January 1, 2030. In consideration for the sale of the Purchased Interest, Blackstone Royalties paid us $1.00 billion.

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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, 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 June 30, 2023, our estimate of this total interest expense resulted in an effective annual interest rate of 8%. 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 June 30, 2023, the carrying value of the liability related to the sale of future royalties was $1.33 billion, net of closing costs of $10.4 million. The carrying value of the liability related to the sale of future royalties approximates fair value as of June 30, 2023 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, 2022	$	1,292,304
Interest expense recognized		51,647
Payments		(11,855)
Carrying value as of June 30, 2023	$	1,332,096

6. 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 June 30, 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	$ 88,264	$ 88,264	$ —	$ —
U.S. treasury securities	7,932	—	7,932	—
Marketable debt securities:				
U.S. treasury securities	729,899	—	729,899	—
U.S. government-sponsored enterprise securities	384,680	—	384,680	—
Corporate notes	158,880	—	158,880	—
Commercial paper	92,577	—	92,577	—
Certificates of deposit	6,415	—	6,415	—
Marketable equity securities	27,256	27,256	—	—
Restricted cash (money market funds)	1,203	1,203	—	—
Total financial assets	$ 1,497,106	$ 116,723	$ 1,380,383	$ —
Financial liabilities				
Development derivative liability	$ 253,963	$ —	$ —	$ 253,963

(In thousands)	As of December 31, 2022	Quoted Prices in Active Markets (Level 1)	Significant Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Financial assets				
Cash equivalents:				
Money market funds	$ 270,394	$ 270,394	$ —	$ —
U.S. treasury securities	44,817	—	44,817	—
U.S. government-sponsored enterprise securities	41,763	—	41,763	—
Commercial paper	22,350	—	22,350	—
Certificates of deposit	3,289	—	3,289	—
Corporate notes	1,024	—	1,024	—
Marketable debt securities:				
U.S. treasury securities	820,913	—	820,913	—
U.S. government-sponsored enterprise securities	230,770	—	230,770	—
Corporate notes	208,284	—	208,284	—
Commercial paper	36,793	—	36,793	—
Certificates of deposit	1,130	—	1,130	—
Marketable equity securities	28,122	28,122	—	—
Restricted cash (money market funds)	1,197	1,197	—	—
Total financial assets	$ 1,710,846	$ 299,713	$ 1,411,133	$ —
Financial liabilities				
Development derivative liability	$ 209,277	$ —	$ —	$ 209,277

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.

7. 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 six months ended June 30, 2023 or 2022.

The following tables summarize our marketable debt securities:

	As of June 30, 2023			
(In thousands)	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
U.S. treasury securities	$ 740,838	$ 26	$ (3,033)	$ 737,831
U.S. government-sponsored enterprise securities	387,754	15	(3,089)	384,680
Corporate notes	160,169	—	(1,289)	158,880
Commercial paper	92,577	—	—	92,577
Certificates of deposit	6,415	—	—	6,415
Total	$ 1,387,753	$ 41	$ (7,411)	$ 1,380,383

	As of December 31, 2022			
(In thousands)	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
U.S. treasury securities	$ 870,033	$ 79	$ (4,382)	$ 865,730
U.S. government-sponsored enterprise securities	275,610	24	(3,101)	272,533
Corporate notes	211,398	16	(2,106)	209,308
Commercial paper	59,143	—	—	59,143
Certificates of deposit	4,419	—	—	4,419
Total	$ 1,420,603	$ 119	$ (9,589)	$ 1,411,133

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

(In thousands)	As of June 30, 2023	As of December 31, 2022
Marketable debt securities	$ 1,372,451	$ 1,297,890
Cash and cash equivalents	7,932	113,243
Total	$ 1,380,383	$ 1,411,133

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8. OTHER BALANCE SHEET DETAILS

Inventory

The components of inventory are summarized as follows:

(In thousands)	As of June 30, 2023	As of December 31, 2022
Raw materials	$ 17,449	$ 22,315
Work in progress	116,661	113,783
Finished goods	28,505	25,606
Total	$ 162,615	$ 161,704

As of June 30, 2023 and December 31, 2022, we had $62.2 million and $32.7 million of long-term inventory, respectively, included within other assets in our condensed consolidated balance sheet as we anticipate it being consumed beyond our normal operating cycle.

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:

	As of June 30,	
(In thousands)	2023	2022
Cash and cash equivalents	$ 657,800	$ 575,558
Total restricted cash included in other assets	2,176	2,177
Total cash, cash equivalents, and restricted cash shown in the condensed consolidated statements of cash flows	$ 659,976	$ 577,735

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) Income
Balance as of December 31, 2022	$ (32,792)	$ (1,092)	$ (9,470)	$ (1,300)	$ (44,654)
Other comprehensive (loss) income before reclassifications	—	—	(11)	5,483	5,472
Amounts reclassified from other comprehensive (loss) income	—	(9)	2,111	—	2,102
Net other comprehensive (loss) income	—	(9)	2,100	5,483	7,574
Balance as of June 30, 2023	$ (32,792)	$ (1,101)	$ (7,370)	$ 4,183	$ (37,080)

(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) Income
Balance as of December 31, 2021	$ (32,792)	$ (2,811)	$ (1,630)	$ 3,974	$ (33,259)
Other comprehensive income (loss) before reclassifications	—	—	4	(83)	(79)
Amounts reclassified from other comprehensive income (loss)	—	69	(8,955)	—	(8,886)
Net other comprehensive income (loss)	—	69	(8,951)	(83)	(8,965)
Balance as of June 30, 2022	$ (32,792)	$ (2,742)	$ (10,581)	$ 3,891	$ (42,224)

Amounts reclassified out of accumulated other comprehensive loss relate to settlements of marketable equity securities and amortization of our pension obligation which are recorded as other income in the condensed consolidated statements of operations and comprehensive loss.

9. CONVERTIBLE DEBT

Convertible Senior Notes Due 2027

On September 12, 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.

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 June 30, 2023, 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 June 30, 2023, the estimated fair value of the Notes was approximately $990.9 million. The fair value was determined based on the last actively traded price per $100 of the Notes for the six months ended June 30, 2023 (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 June 30, 2023, the effective interest rate of the Notes is 1%.

Capped Call Transactions

In September 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. We used approximately $118.6 million of the proceeds from the offering of Notes to pay the cost of the Capped Call Transactions.

We evaluated the Capped Call Transactions and determined that they should be accounted for separately from the Notes. The cost of $118.6 million to purchase the Capped Call Transactions was recorded as a reduction to additional paid-in capital in the condensed consolidated balance sheet as of June 30, 2023 as the Capped Call Transactions are indexed to our own stock and met the criteria to be classified in stockholders' deficit.

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. 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 it 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. 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.

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-cardiomyopathy following termination.

We account for the Funding Agreement under ASC Topic 815, Derivatives and Hedging, as a derivative liability, measured at fair value, within other liabilities on our condensed consolidated balance sheets. 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 June 30, 2023, 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-cardiomyopathy, (iv) our cost of borrowing (12%), and (v) Blackstone Life Sciences' cost of borrowing (4%).

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

Carrying value as of December 31, 2022	$	209,277
Amount received under the Funding Agreement		8,000
Change in fair value of development derivative liability		36,686
Carrying value as of June 30, 2023	$	253,963

11. STOCK-BASED COMPENSATION

The following table summarizes stock-based compensation expenses included in operating costs and expenses:

	Three Months Ended June 30,		Six Months Ended June 30,	
(In thousands)	2023	2022	2023	2022
Research and development	$ 32,801	$ 10,638	$ 49,033	$ 22,255
Selling, general and administrative	43,001	19,833	66,716	37,509
Total	$ 75,802	$ 30,471	$ 115,749	$ 59,764

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 would be 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 all periods presented, 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:

	As of June 30,	
(In thousands)	2023	2022
Options to purchase common stock, inclusive of performance-based stock options	8,023	12,719
Unvested restricted stock units, inclusive of performance-based restricted stock units	2,303	1,950
Convertible debt	3,616	—
Total	13,942	14,669

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 June 30, 2023, 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.

Government Investigation

We previously disclosed that, in April 2021, we received a subpoena from the U.S. Department of Justice, U.S. Attorney's Office for the District of Massachusetts, requiring production of documents pertaining to our marketing and promotion of ONPATTRO (patisiran) in the U.S. We responded to the subpoena and cooperated with the U.S. Attorney's Office's requests. On August 1, 2023, the U.S. Attorney's Office informed us that it planned to close its investigation into this matter.

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.

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 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 infringing our newly granted U.S. Patent No. 11,382,979 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 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 new lawsuits against Pfizer and Moderna in Delaware seeking damages for infringing the '229 patent. In addition to this patent, we added recently granted U.S. Patent Nos. 11,633,479 and 11,633,480 in the newly filed suits against both Pfizer and Moderna and also U.S. Patent No. 11,612,657 against Pfizer only.

The court has set a trial date for the previously filed cases of November 12, 2024, for Alnylam v. Moderna and November 18, 2024, for Alnylam v. Pfizer/BioNTech. The recently filed lawsuits in May 2023 are pending before the court with no trial date set.

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, including, for example, the recently closed government investigation, 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 June 30, 2023.

14. SUBSEQUENT EVENT

On July 21, 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 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 will make an upfront payment of $310.0 million under the Roche Collaboration and License Agreement. In addition, we will be eligible to receive up to $2.50 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.

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, and 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 *Alnylam P^{5}x25* strategy, which focuses on our planned transition to a top-tier biotech company by the end of 2025. With *Alnylam P^{5}x25*, we aim to deliver transformative rare and 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 four Strategic Therapeutic Areas, or "STArs:" Genetic Medicines; Cardio-Metabolic Diseases; Hepatic Infectious Diseases; and CNS/Ocular Diseases. Four of our marketed products are within the Genetic Medicines STAr, ONPATTRO, AMVUTTRA, GIVLAARI and OXLUMO.

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 transthyretin amyloidosis, or ATTR amyloidosis, with cardiomyopathy, and in December 2022, we submitted a supplemental New Drug Application, or sNDA, to the FDA for ONPATTRO as a potential treatment of the cardiomyopathy of ATTR amyloidosis. In February 2023, the FDA accepted the sNDA for filing and set an action date of October 8, 2023 under the Prescription Drug User Fee Act, or PDUFA. The FDA also indicated in the sNDA filing communication letter that it planned to hold an advisory committee meeting to discuss the application, and in July 2023, the FDA announced that an advisory committee meeting has been scheduled for September 13, 2023 to review the sNDA. In March 2023, we submitted an sNDA to the Brazilian Health Regulatory Agency (ANVISA) for ONPATTRO for the treatment of the cardiomyopathy of ATTR amyloidosis.

AMVUTTRA is approved in the U.S. for the treatment of the polyneuropathy of hATTR amyloidosis in adults. In September 2022, AMVUTTRA was granted marketing authorization in Europe and the United Kingdom, or UK, for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of TTR type familial amyloidosis with polyneuropathy. In December 2022, AMVUTTRA was approved in Brazil for the treatment of hATTR amyloidosis in adults. Regulatory filings in other territories are currently under review and additional filings are pending or planned during 2023 and beyond.

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 additional countries, including Brazil, Canada, Switzerland and Japan. Regulatory filings for givosiran (the non-branded drug name for GIVLAARI) in other territories are pending or planned during 2023 and beyond.

OXLUMO is approved in the U.S. and EU for the treatment of primary hyperoxaluria type 1, or PH1, in all age groups, and in several additional countries including Brazil and Switzerland. In October 2022, we announced that the FDA approved our sNDA for lumasiran (the non-branded drug name for OXLUMO) for the treatment of PH1 to lower urinary oxalate and plasma oxalate levels in pediatric and adult patients. Regulatory filings in other territories are pending and additional filings are planned during 2023 and beyond.

Our fifth product, Leqvio (inclisiran), is in the Cardio-Metabolic Diseases STAr. Leqvio is being developed and commercialized by our partner 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 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. As of June 30, 2023, Leqvio has been approved in more than 80 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: patisiran (the non-branded drug name for ONPATTRO) for the treatment of ATTR (wild-type or hereditary) amyloidosis with cardiomyopathy; vutrisiran (the non-branded drug name for AMVUTTRA) for the treatment of ATTR (wild-type or hereditary) amyloidosis with cardiomyopathy; as well as fitusiran for the treatment of hemophilia, which is being advanced by our partner Genzyme Corporation, a Sanofi Company, or Sanofi; and cemdisiran for the treatment of complement-mediated diseases, where our partner 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 *Alnylam P^{5}x25* strategy, we have multiple drivers of future growth, including the development of transformative prevalent disease medicines. 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 November 2021, we reported positive interim data from the ongoing Phase 1 study of zilebesiran, and initiated the KARDIA Phase 2 clinical studies for zilebesiran. KARDIA-1 is designed to evaluate zilebesiran as a monotherapy across different doses administered quarterly and biannually. KARDIA-2 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 January 2023, we announced that we completed enrollment of patients in the KARDIA-1 Phase 2 study and in July 2023, we announced that we completed enrollment of patients in the KARDIA-2 Phase 2 study. Topline results from the KARDIA-1 and KARDIA-2 Phase 2 studies are anticipated in mid-2023 and early 2024, respectively. In July 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 of zilebesiran. A description of our collaboration with Roche is described in more detail below under the heading “Strategic Alliances.”

We are also advancing ALN-APP, an investigational RNAi therapeutic targeting amyloid precursor protein in development for the treatment of Alzheimer’s disease and cerebral amyloid angiopathy. In April 2023 and in July 2023, we reported positive interim results from the ongoing single ascending dose part of the Phase 1 study of ALN-APP 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 *Alnylam P^{5}x25* 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 maintain focus on our global compliance program to drive its evolution and enhancement in view of the *Alnylam P^{5}x25 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 alliances with leading pharmaceutical and life sciences companies to support our development and commercialization efforts, including Regeneron, Roche, Novartis (which acquired our partner The Medicines Company, or MDCO, in 2020), Sanofi, Vir Biotechnology, Inc., or Vir, Dicerna Pharmaceuticals, Inc. (acquired by Novo Nordisk A/S, or Novo Nordisk, in December 2021), or Dicerna, and PeptiDream, Inc., or PeptiDream.

We have incurred significant losses since we commenced operations in 2002 and as of June 30, 2023, we had an accumulated deficit of $7.02 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, however we expect 2019 represents our peak operating loss year as we transition towards a self-sustainable financial profile. 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 June 30, 2023, we generate worldwide product revenues from four commercialized products, ONPATTRO, AMVUTTRA, GIVLAARI and OXLUMO, primarily in the U.S., Europe and Japan. 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 approved products or any other products approved in the future. A portion of our total revenues in recent years has been derived from collaboration revenues from strategic alliances with Regeneron, Vir 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 alliances. Such alliances 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 partner Novartis, as well as proceeds from the sale of equity or debt.

Convertible Senior Notes

In September 2022, we issued $1.04 billion aggregate principal amount of 1.00% Convertible Senior Notes due 2027, or Notes. The Notes will mature on September 15, 2027, unless earlier converted, redeemed or repurchased. Before June 15, 2027, noteholders will have the right to convert their Notes in certain circumstances and during specified periods. From and after June 15, 2027, the Notes will be convertible at the option of the noteholders at any time prior to the close of business on the second scheduled trading day immediately preceding the maturity date. 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 our common stock, at our election.

In connection with the issuance of the Notes, we paid $118.6 million, including expenses, to enter into privately negotiated capped call transactions with certain initial purchasers of the Notes or their respective affiliates and certain other financial institutions, or capped call transactions. The capped call transactions are expected generally to reduce the potential dilution upon conversion of the Notes in the event that the market price per share of our common stock, as measured under the terms of the capped call transactions, is greater than the strike price of the capped call transactions, which initially corresponds to the conversion price of the Notes, and is subject to anti-dilution adjustments generally similar to those applicable to the conversion rate of the Notes. The cap price of the capped call transactions will initially be $424.00 per share, which represents a premium of approximately 100% based on the last reported sale price of our 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. If, however, the market price per share of our common stock, as measured under the terms of the capped call transactions, exceeds the cap price of the capped call transactions, there would nevertheless be dilution upon conversion of the Notes to the extent that such market price exceeds the cap price of the capped call transactions.

We used approximately $762.0 million of the net proceeds from the offering of the Notes to repay borrowings, inclusive of prepayment premiums, under our credit agreement with Blackstone, with the remaining net proceeds designated for general corporate purposes.

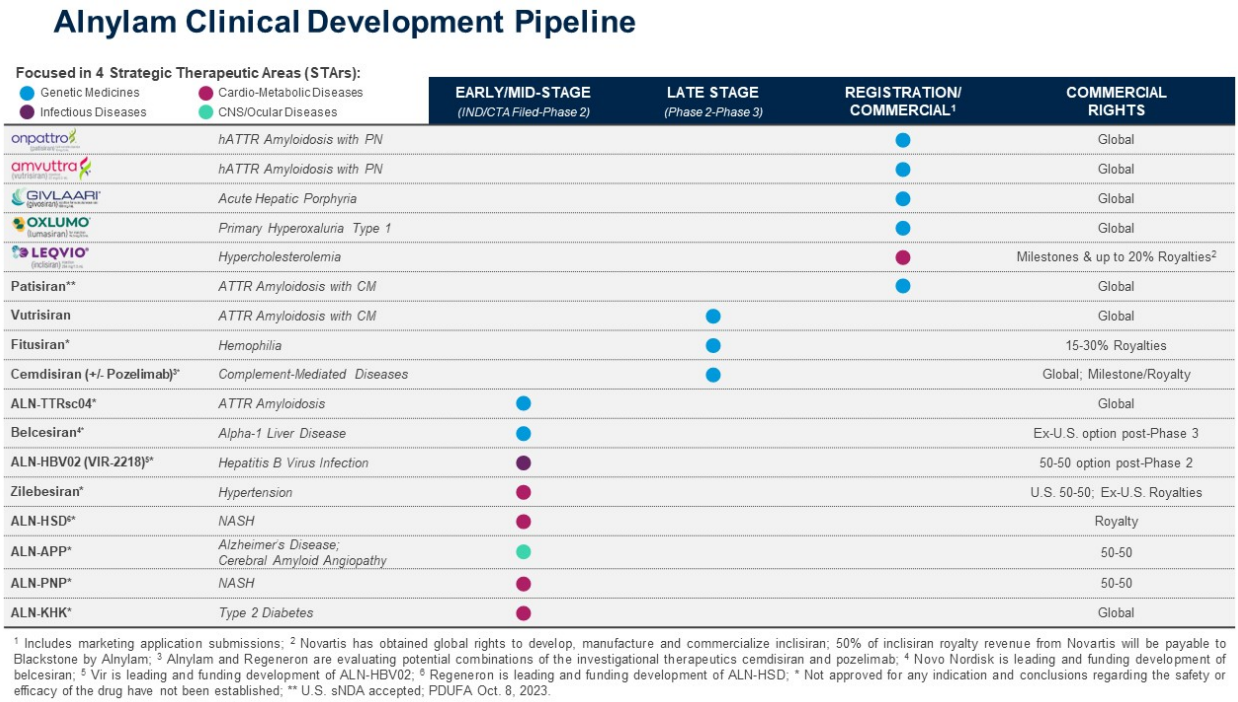
Research and Development

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, is focused in four STArs: Genetic Medicines; Cardio-Metabolic Diseases; Hepatic Infectious Diseases; and CNS/Ocular Diseases.

The chart below is a summary of our commercial products and late- and early-stage development programs as of July 31, 2023. It identifies those programs for which we have received marketing approval, the stage of our programs and our commercial rights to such programs:



During the second quarter of 2023 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 second quarter of 2023 of $91.5 million and $132.1 million, respectively.

Total Ultra-Rare: GIVLAARI & OXLUMO

- We achieved global net product revenues for GIVLAARI and OXLUMO for the second quarter of 2023 of $57.9 million and $24.2 million, respectively.

Leqvio

- Our partner, Novartis, continued the launch of Leqvio in the U.S. and in other markets, with focus on patient on-boarding, removing access hurdles and enhancing medical education.
- Novartis announced that the FDA approved a label update for Leqvio to enable earlier use in patients with elevated LDL-C who have an increased risk of heart disease, as an adjunct to diet and statin therapy.

Late-Stage Clinical Development

- Presented new results from an interim analysis of data from the open-label extension period of the APOLLO-B Phase 3 study of patisiran, demonstrating continued evidence of sustained benefit across measures of functional capacity and

health status and quality of life, as well as cardiac stress and injury. Patisiran demonstrated a safety profile consistent with that observed in the 12-month double-blind period, with no new safety findings.

  - Submitted 18-month data from the APOLLO-B Phase 3 study to the FDA as part of the sNDA review for patisiran for the treatment of the cardiomyopathy of ATTR amyloidosis.
  - Announced that the FDA has set a date of September 13, 2023 for the meeting of the Cardiovascular and Renal Drugs Advisory Committee to review the sNDA for patisiran.

- Completed enrollment in the KARDIA-2 Phase 2 study, evaluating the safety and efficacy of zilebesiran in patients with uncontrolled hypertension when added on top of another antihypertensive medication, with topline results expected in early 2024.

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 Alliances

Our business strategy is to develop and commercialize a broad pipeline of RNAi therapeutic products directed towards our four STArs. As part of this strategy, we have entered into, and expect to enter into additional, collaboration and licensing agreements as a means of obtaining resources, capabilities and funding to advance our investigational RNAi therapeutic programs.

Our collaboration strategy is to form alliances that create significant value for ourselves and our collaborators in the advancement of RNAi therapeutics as a new class of innovative medicines. Specifically, with respect to our CNS/Ocular Disease pipeline, 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 disease targets expressed in the eye and CNS, in addition to a select number of targets expressed in the liver. In July 2020, Regeneron exercised its co-development/co-commercialization option on our first CNS-targeted development candidate, ALN-APP, 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.

With respect to our Cardio-Metabolic pipeline, in March 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 inclisiran. In March 2018, we entered into a discovery collaboration with Regeneron to identify RNAi therapeutics for nonalcoholic steatohepatitis, or NASH, and potentially other related diseases, and in November 2018, we and Regeneron entered into a separate, fifty-fifty collaboration to further research, co-develop and commercialize any therapeutic product candidates that emerge from these discovery efforts. In April 2020, we entered into a development and commercialization collaboration with Dicerna to advance investigational RNAi therapeutics for the treatment of alpha-1 antitrypsin deficiency-associated liver disease, or alpha-1 liver disease.

In addition, 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 will make an upfront payment of $310.0 million under the Roche Collaboration and License Agreement. In addition, we will be eligible to receive up to $2.50 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.

With respect to our Hepatic Infectious Disease pipeline, in October 2017, we announced an exclusive licensing agreement with Vir for the development and commercialization of RNAi therapeutics for infectious diseases, including chronic HBV infection. In March 2020, we announced an expansion of our exclusive licensing agreement with Vir to include the development and commercialization of RNAi therapeutics targeting SARS-CoV-2, the virus that causes the disease COVID-19, which we further expanded in April 2020 to include up to three additional targets focused on host factors for SARS-CoV-2, including angiotensin converting enzyme-2, and transmembrane protease, serine 2, and potentially a third mutually selected host factor target. In July 2021, we notified Vir that we elected to discontinue ALN-COV, in development for the treatment of COVID-19, and all other COVID-19 research and development activities, based on a portfolio prioritization in view of the availability of highly effective vaccines and alternative treatment options. Following such discontinuation of COVID-19 related activities, we have no further obligations to work on the COVID-related targets and Vir has no further rights to such targets under our exclusive licensing agreement.

With respect to our Genetic Medicine pipeline, 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.

We intend to continue to evaluate and explore partnership opportunities through collaboration and licensing arrangements, and may enter into new collaborations to advance certain products or disease areas. For example, in January 2022, we announced that we and Novartis agreed to collaborate on the discovery and development of an siRNA-based targeted therapy to restore functional liver cells in patients with end-stage liver diseases.

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. For example, in 2021, we entered into a license and collaboration agreement with PeptiDream to discover and develop peptide-siRNA conjugates leveraging PeptiDream's proprietary Peptide Discovery Platform System technology.

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, 2022, which we filed with the SEC on February 23, 2023. 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:

	Three Months Ended June 30,				Six Months Ended June 30,			
(In thousands, except percentages)	**2023**	**2022**	**$ Change**	**% Change**	**2023**	**2022**	**$ Change**	**% Change**
Total revenues	$ 318,754	$ 224,818	$ 93,936	42 %	$ 638,044	$ 438,077	$ 199,967	46 %
Operating costs and expenses	$ 548,585	$ 416,504	$ 132,081	32 %	$ 1,017,682	$ 776,495	$ 241,187	31 %
Loss from operations	$ (229,831)	$ (191,686)	$ (38,145)	20 %	$ (379,638)	$ (338,418)	$ (41,220)	12 %
Net loss	$ (276,024)	$ (277,402)	$ 1,378	(0.5)%	$ (450,125)	$ (517,743)	$ 67,618	(13)%

Discussion of Results of Operations

Revenues

Total revenues consist of the following:

(In thousands, except percentages)	Three Months Ended June 30, 2023	2022	$ Change	% Change	Six Months Ended June 30, 2023	2022	$ Change	% Change
Net product revenues	$ 305,705	$ 213,515	$ 92,190	43 %	$ 582,033	$ 400,387	$ 181,646	45 %
Net revenues from collaborations	5,844	9,025	(3,181)	(35)%	42,306	34,970	7,336	21 %
Royalty revenue	7,205	2,278	4,927	216 %	13,705	2,720	10,985	404 %
Total	$ 318,754	$ 224,818	$ 93,936	42 %	$ 638,044	$ 438,077	$ 199,967	46 %

Net Product Revenues

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

(In thousands, except percentages)	Three Months Ended June 30, 2023	2022	$ Change	% Change	Six Months Ended June 30, 2023	2022	$ Change	% Change
ONPATTRO								
United States	$ 25,560	$ 71,085	$ (45,525)	(64)%	$ 55,377	$ 133,392	$ (78,015)	(58)%
Europe	56,393	56,787	(394)	(1)%	116,071	109,968	6,103	6 %
Rest of World	9,505	25,556	(16,051)	(63)%	22,503	47,077	(24,574)	(52)%
Total	91,458	153,428	(61,970)	(40)%	193,951	290,437	(96,486)	(33)%
AMVUTTRA								
United States	96,469	—	96,469	N/A	175,482	—	175,482	N/A
Europe	14,405	—	14,405	N/A	21,173	—	21,173	N/A
Rest of World	21,262	—	21,262	N/A	37,249	—	37,249	N/A
Total	132,136	—	132,136	N/A	233,904	—	233,904	N/A
GIVLAARI								
United States	35,196	29,661	5,535	19 %	65,487	53,336	12,151	23 %
Europe	14,051	13,894	157	1 %	28,522	23,582	4,940	21 %
Rest of World	8,652	1,595	7,057	442 %	11,796	3,509	8,287	236 %
Total	57,899	45,150	12,749	28 %	105,805	80,427	25,378	32 %
OXLUMO								
United States	8,794	7,121	1,673	23 %	17,851	12,533	5,318	42 %
Europe	12,216	7,593	4,623	61 %	25,525	15,751	9,774	62 %
Rest of World	3,202	223	2,979	1336 %	4,997	1,239	3,758	303 %
Total	24,212	14,937	9,275	62 %	48,373	29,523	18,850	64 %
Total net product revenues	$ 305,705	$ 213,515	$ 92,190	43 %	$ 582,033	$ 400,387	$ 181,646	45 %

Net product revenues increased during the three and six months ended June 30, 2023, compared to the same periods in 2022, primarily due to the launch of AMVUTTRA in the third quarter of 2022, partially offset by a decrease of demand for ONPATTRO due to patient switches to AMVUTTRA. Additional growth was provided by an increase in patients on GIVLAARI and OXLUMO therapies. Growth in our Rest of World markets was also driven, in part, by the timing of orders in some of those markets.

We expect net product revenues to increase during 2023, as compared to 2022, as we continue to add new patients onto our commercial products, as well as launch these products into additional markets, assuming regulatory approvals.

Net Revenues from Collaborations and Royalty Revenue

Net revenues from collaborations consist of the following:

	Three Months Ended June 30,				Six Months Ended June 30,			
(In thousands, except percentages)	**2023**	**2022**	**$ Change**	**% Change**	**2023**	**2022**	**$ Change**	**% Change**
Regeneron Pharmaceuticals	$ (2,837)	$ 14	$ (2,851)	(20364)%	$ 17,153	$ 12,426	$ 4,727	38 %
Novartis AG	8,627	8,533	94	1 %	23,560	21,669	1,891	9 %
Other	54	478	(424)	(89)%	1,593	875	718	82 %
Total	$ 5,844	$ 9,025	$ (3,181)	(35)%	$ 42,306	$ 34,970	$ 7,336	21 %

Net revenues from collaborations decreased during the three months ended June 30, 2023, as compared to the same period in 2022, primarily driven by revised assumptions for and expected future cost associated with our collaboration with Regeneron. These changes increased the total forecasted costs to be incurred over the program and reduced the measure of progress resulting in a reversal of revenue.

Net revenues from collaborations increased during the six months ended June 30, 2023, as compared to the same period in 2022, primarily due to an increase in activity under our licensed programs within the Regeneron collaboration.

Royalty revenue increased during the three and six months ended June 30, 2023, as compared to the same period in 2022, due to increased royalties earned from global net sales of Leqvio by our partner, 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 partners, achievement of milestones under our collaboration agreements, and royalties associated with sales of Leqvio. We expect variability in net revenues from collaboration and royalty revenue in 2023, as compared to 2022, due to the timing of manufacturing activities, achievement of milestones under our collaboration agreements, and royalties associated with sales of Leqvio.

Operating Costs and Expenses

Operating costs and expenses consist of the following:

	Three Months Ended June 30,				Six Months Ended June 30,			
(In thousands, except percentages)	**2023**	**2022**	**$ Change**	**% Change**	**2023**	**2022**	**$ Change**	**% Change**
Cost of goods sold	$ 75,336	$ 34,038	$ 41,298	121 %	$ 116,768	$ 57,495	$ 59,273	103 %
Cost of goods sold as a percentage of net product revenues	*24.6 %*	*15.9 %*			*20.1 %*	*14.4 %*		
Cost of collaborations and royalties	10,034	6,770	3,264	48 %	23,471	18,940	4,531	24 %
Research and development	248,526	205,712	42,814	21 %	479,095	375,605	103,490	28 %
Selling, general and administrative	214,689	169,984	44,705	26 %	398,348	324,455	73,893	23 %
Total	$ 548,585	$ 416,504	$ 132,081	32 %	$ 1,017,682	$ 776,495	$ 241,187	31 %

Cost of goods sold

Cost of goods sold as a percentage of net product revenues increased during the three and six months ended June 30, 2023, as compared to the same periods in 2022, primarily due to cancelling manufacturing commitments for ONPATTRO and other adjustments to inventory. Demand for ONPATTRO decreased during the three and six months ended June 30, 2023 as ongoing patients continue to switch to AMVUTTRA. Costs of goods sold as a percentage of net product revenues also increased as royalties owed to third parties increased as sales of AMVUTTRA were higher year-over-year. These increases were offset by lower manufacturing costs for AMVUTTRA compared with ONPATTRO.

We expect cost of goods sold and cost of goods sold as a percentage of net product revenues will increase during 2023, as compared to 2022, primarily as a result of an expected increase in total net product sales and increased AMVUTTRA royalties. Furthermore, we could experience further adjustments to inventory and facilities as global demand for ONPATTRO continues to fluctuate.

Cost of collaborations and royalties

Cost of collaborations and royalties increased during the three and six months ended June 30, 2023, as compared to the same periods in 2022, primarily due to increased collaboration revenue and timing and demand of GalNAc material supply to our collaboration partners to support certain product manufacturing and ongoing clinical trials.

We anticipate an increase in the cost of collaborations and royalties during 2023, as compared to 2022, due to the timing and demand of GalNAc material to be supplied to our collaboration partners.

Research and development

Research and development expenses consist of the following:

	Three Months Ended June 30,				Six Months Ended June 30,			
(In thousands, except percentages)	**2023**	**2022**	**$ Change**	**% Change**	**2023**	**2022**	**$ Change**	**% Change**
Clinical research and outside services	$ 109,698	$ 107,191	$ 2,507	2 %	$ 221,295	$ 184,071	$ 37,224	20 %
Compensation and related	64,707	53,739	10,968	20 %	129,427	105,039	24,388	23 %
Occupancy and all other costs	41,320	34,144	7,176	21 %	79,340	64,240	15,100	24 %
Stock-based compensation	32,801	10,638	22,163	208 %	49,033	22,255	26,778	120 %
Total	$ 248,526	$ 205,712	$ 42,814	21 %	$ 479,095	$ 375,605	$ 103,490	28 %

For the three and six months ended June 30, 2023, the increase in research and development expenses, as compared to the same periods in 2022, was primarily due to the following:

- Increased clinical research and outside services associated with the KARDIA-1/KARDIA-2 (zilebesiran) clinical studies and manufacturing related expenses associated with our pre-clinical activities;
- Increased stock-based compensation expense primarily due to the accounting for certain performance-based awards;
- Increased compensation and related expenses as a result of increased headcount to support our R&D pipeline and development expenses; and
- Increased occupancy and all other costs as a result of increased infrastructure costs associated with our research facilities.

During the three and six months ended June 30, 2023 and 2022, in connection with advancing activities under our collaboration agreements, we incurred research and development expenses, primarily related to external development and clinical expenses, 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 collaboration partner:

	Three Months Ended June 30,		Six Months Ended June 30,	
(In thousands)	**2023**	**2022**	**2023**	**2022**
Regeneron Pharmaceuticals	$ 20,196	$ 11,687	$ 39,315	$ 23,054
Other	548	457	1,346	815
Total	$ 20,744	$ 12,144	$ 40,661	$ 23,869

Selling, general and administrative

Selling, general and administrative expenses consist of the following:

	Three Months Ended June 30,				Six Months Ended June 30,			
(In thousands, except percentages)	**2023**	**2022**	**$ Change**	**% Change**	**2023**	**2022**	**$ Change**	**% Change**
Compensation and related	$ 75,507	$ 66,702	$ 8,805	13 %	$ 149,833	$ 126,985	$ 22,848	18 %
Consulting and professional services	57,848	51,120	6,728	13 %	108,536	95,581	12,955	14 %
Occupancy and all other costs	38,333	32,329	6,004	19 %	73,263	64,380	8,883	14 %
Stock-based compensation	43,001	19,833	23,168	117 %	66,716	37,509	29,207	78 %
Total	$ 214,689	$ 169,984	$ 44,705	26 %	$ 398,348	$ 324,455	$ 73,893	23 %

For the three and six months ended June 30, 2023, the increase in selling, general and administrative expenses, as compared to the same periods in 2022, was primarily due to the following:

- Increased stock-based compensation expense primarily due to the accounting for certain performance-based awards;
- Increased compensation and related expenses as a result of increased headcount and other strategic investments in support of the global launch of AMVUTTRA and other expenses to support our strategic growth; and
- Increased consulting and professional services primarily driven by the global launch of AMVUTTRA.

We expect that research and development expenses combined with selling, general and administrative expenses will increase during 2023, as compared to 2022, as we continue to advance and develop our platform and pipeline, advance our product candidates, including partnered programs, into later-stage development, prepare regulatory submissions and continue to build-out our global commercial and compliance infrastructure and field team to support our commercial portfolio 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:

	Three Months Ended June 30,				Six Months Ended June 30,			
(In thousands, except percentages)	**2023**	**2022**	**$ Change**	**% Change**	**2023**	**2022**	**$ Change**	**% Change**
Interest expense	$ (30,035)	$ (42,609)	$ 12,574	(30)%	$ (58,990)	$ (84,971)	$ 25,981	(31)%
Interest income	21,075	1,899	19,176	1010 %	39,730	2,911	36,819	1265 %
Other expense, net								
Realized and unrealized gain (losses) on marketable equity securities	1,400	(1,097)	2,497	(228)%	(867)	(32,258)	31,391	(97)%
Change in fair value of development derivative liability	(30,215)	(31,910)	1,695	(5)%	(36,686)	(45,692)	9,006	(20)%
Other	(6,603)	(9,270)	2,667	(29)%	(10,120)	(15,601)	5,481	(35)%
Total	$ (44,378)	$ (82,987)	$ 38,609	(47)%	$ (66,933)	$ (175,611)	$ 108,678	(62)%

Total other expense decreased during the three and six months ended June 30, 2023, as compared to the same periods in 2022, primarily due to the following:

- Increased interest income driven by higher market interest rates on our marketable debt securities;
- Decreased interest expense as a result of a more favorable interest rate under the Notes compared with the interest rate under the credit facility held with Blackstone as executed and extinguished in September 2022, respectively; and
- Decreased realized and unrealized losses on our marketable equity securities holdings.

Liquidity and Capital Resources

The following table summarizes our cash flow activities:

	Six Months Ended June 30,	
(In thousands)	**2023**	**2022**
Net cash (used in) provided by:		
Operating activities	$ (225,461)	$ (294,012)
Investing activities	$ (84,930)	$ (4,626)
Financing activities	$ 99,765	$ 65,293

Operating activities

Net cash used in operating activities decreased during the six months ended June 30, 2023, compared to the same period ended 2022, primarily due to stronger cash receipts from increased product sales.

Investing activities

Net cash used in investing activities decreased during the six months ended June 30, 2023, compared to the same period ended 2022, primarily due to net activities related to our marketable debt securities.

Financing activities

Net cash provided by financing activities increased during the six months ended June 30, 2023, compared to the same period ended 2022, primarily due to increased net proceeds from the issuance of common stock in connection with stock option exercises and other types of equity.

Additional Capital Requirements

We currently have programs focused on a number of therapeutic areas and, as of June 30, 2023, 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 ONPATTRO and 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 2022 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 June 30, 2023, 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 2022 Annual Report on Form 10-K.

Based on our current operating plan, we believe that our cash, cash equivalents and marketable securities as of June 30, 2023, 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 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, 2022. As of June 30, 2023, there have been no significant changes to the financial market risks described as of December 31, 2022. 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 June 30, 2023. 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 June 30, 2023, 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 June 30, 2023 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

We operate in an environment that involves a number of significant risks and uncertainties. We caution you to read the following risk factors, which have affected, and/or in the future could affect, our business, prospects, operating results, and financial condition. The risks described below include forward-looking statements, and actual events and our actual results may differ materially from these forward-looking statements. Additional risks and uncertainties not currently known to us or that we currently deem immaterial may also impair our business, prospects, operating results, and financial condition. Furthermore, additional risks and uncertainties are described under other captions in this report and should also be considered by our investors.

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 indications for ONPATTRO and AMVUTTRA.
- We have a history of losses and may never become and remain consistently profitable.
- We will require substantial funds to continue our research, development and commercialization activities.
- Any future outbreaks of COVID-19 and its variants, or other highly infectious or contagious diseases, may directly or indirectly adversely affect our business, results of operations and financial condition.
- Although we sold a portion of the expected royalty stream and commercial milestones related to global sales of Leqvio by Novartis, we are entitled to retain the remaining portion of such future royalties and, if certain specified thresholds are met, to the remaining portion of commercial milestone payments, and any negative developments related to Leqvio could have a material adverse effect on the timing or amount of those payments.

Risks Related to Our Dependence on Third Parties

- We may not be able to execute our business strategy if we are unable to maintain existing or enter into new alliances 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 and we could suffer other economic harm.
- 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 they 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 candidates we or our partners develop may fail in development or be delayed to a point where they do not become commercially viable.
- We or our partners may be unable to obtain U.S. or foreign regulatory approval for our or our partnered product candidates, or if approved, may fail to obtain desired labeling for such products.
- Even if we or our partners obtain regulatory approvals, our marketed drugs will be subject to ongoing regulatory oversight.
- Even if we receive regulatory approval to market our product candidates, and our collaborators receive regulatory approval to market product candidates discovered by us or developed with our technology, 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 scale our marketing, sales, market access and distribution capabilities and further establish our global commercial and compliance infrastructure, and our commercial efforts may not be successful.
- We may incur significant liability if enforcement authorities allege or determine that we are engaging in commercial activities or promoting our commercially approved products in a way that violates applicable regulations.
- Any drugs we develop 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 and business prospects 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., 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 RNAi technology.

Risks Related to Competition

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

Risks Related to Our Common Stock

- If our stock price fluctuates, purchasers of our common stock could incur substantial losses.
- We may incur significant costs from class action litigation.
- Future sales of shares of our common stock, including by our significant stockholders, us or our directors and officers, could cause the price of our common stock to decline.

Risks Related to Our Convertible Notes

- Servicing our debt may require a significant amount of cash. 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 the Notes or to repurchase the Notes for cash upon a fundamental change, and our future debt may contain limitations on our ability to pay cash upon conversion of the Notes or to repurchase the Notes.
- The conditional conversion feature of the Notes, if triggered, may adversely affect our financial condition and operating results.

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 less successful than anticipated, and we may be unable to expand the indications for ONPATTRO and AMVUTTRA.

In 2018, our first commercial product, ONPATTRO, was approved by the FDA and EMA, and we have since received approval and launched ONPATTRO in several additional territories. In 2019, the FDA approved our second product, GIVLAARI, which was also approved by the EMA and has since received approval in several additional territories, and in 2020, the FDA and EMA approved our third product, OXLUMO, which received additional regulatory approvals in 2021 and 2022. In June 2022, the FDA approved AMVUTTRA, which was granted marketing authorization in Europe and the UK in September 2022 and has since received regulatory approval in Japan and Brazil. We also have multiple product candidates in late-stage clinical development. While we have commercially launched four products, we cannot predict whether we will successfully market and sell our approved products, or successfully expand the indications of certain of our approved products, including ONPATTRO and 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 and submitted an sNDA to the FDA that was accepted for review in February 2023, we cannot be certain that the results from the APOLLO-B clinical trial will support regulatory approval of patisiran for the treatment of patients with ATTR amyloidosis with cardiomyopathy.

To execute our business plan of building a profitable, top-tier biotech company over the next 5 years and achieving our *Alnylam P^{5}x25* strategy and the metrics associated with such strategy, in addition to successfully marketing, selling and expanding the 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 and muscle;
- build and maintain a strong intellectual property portfolio;
- gain regulatory acceptance for the development and commercialization of our product candidates and market success for our approved products, as well as any other products we commercialize;
- attract and retain customers for our products;
- develop and maintain successful strategic alliances; 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 consistently profitable.

We have experienced significant operating losses since our inception. As of June 30, 2023, we had an accumulated deficit of $7.02 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 2023 and beyond, we may never attain profitability or positive cash flow from operations. For the three and six months ended June 30, 2023, we recognized $305.7 million and $582.0 million, respectively, 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 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 current alliances, 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 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 alliances with pharmaceutical and biotechnology companies, including Roche, Novartis and Regeneron. We cannot be certain that we will be

able to maintain our existing alliances, secure and maintain new alliances, meet the obligations, or achieve any milestones that we may be required to meet or achieve to receive payments under our existing or new alliances. Moreover, we cannot be certain that our partners, including Novartis, will continue to successfully execute their obligations under our alliance agreements and generate additional revenues for us.

We believe that to become and remain consistently profitable, we must succeed in discovering, developing and commercializing novel drugs 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 these novel drugs and manufacturing, marketing and selling them. 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 the funds we require are greater than what we have estimated, we may need to critically limit or significantly scale back or cease certain of our activities.

We have used substantial funds to develop our RNAi technologies and will require substantial funds to conduct further research and development, 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 activities associated with successful development of our product candidates, including zilebesiran, may be greater than we anticipate, we are unable to estimate the actual funds we will require to develop and commercialize them.

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 alliances, including milestones and royalties on Leqvio sales, will enable us to achieve a self-sustainable financial profile without need for future equity financing. However, our future capital requirements and the period for which we expect our existing resources to support our operations may vary from what we 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 bodies to advance these programs;
- the timing, receipt and amount of milestone and other payments, if any, from present and future collaborators, if any, including milestones from Roche with respect to the development or commercialization of zilebesiran, as well as milestone payments related to Leqvio, which is being commercialized by our partner, Novartis;
- our ability to maintain and establish additional collaborative arrangements 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 commercial sale;
- the impact of any future pandemics or public health emergencies or the ongoing conflict in 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 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 drug 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 are unable to obtain additional 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.

Any future outbreaks of COVID-19 and its variants, or other highly infectious or contagious diseases, may directly or indirectly adversely affect our business, results of operations and financial condition.

In the future, we may experience disruptions from COVID-19 or a future 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 the COVID-19 or a future pandemic or public health emergency. Business interruptions from future 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 partners 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 the COVID-19 pandemic or any future 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 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 2023.

Health regulatory agencies globally may also experience disruptions in their operations as a result of the COVID-19 pandemic or future public health emergencies, which could impact review, inspection and approval timelines. Since March 2020, when foreign and domestic inspections of facilities were largely placed on hold, 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 COVID-19, or any future 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 COVID-19, or any future 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.

Although we sold a portion of the royalty stream and commercial milestones from the global sales of Leqvio by our collaborator, Novartis, we are entitled to retain the remaining portion of future royalties from the global sales of Leqvio and, if certain specified thresholds are met, to the remaining portion of commercial milestone payments, 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 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 royalty interest will increase to 55% effective January 1, 2030. Our receipt of future royalty payments and a portion of commercial milestone payments may be negatively impacted if the Leqvio royalty stream and commercial milestones payments are insufficient to meet the specified thresholds. Any negative impact to future royalty payments and

commercial milestone payments could affect our ability to meet the specified repayment thresholds. Additional factors that may have an adverse effect on the Leqvio royalty stream and commercial milestones include:

- companies working to develop new therapies or alternative formulations of products for ASCVD;
- foreign currency exchange rate fluctuations, which could have a negative impact on Novartis' sales of Leqvio, thereby reducing the royalties;
- any negative developments relating to Leqvio, such as safety, efficacy, or reimbursement issues, could reduce demand for Leqvio;
- any disputes concerning patents, proprietary rights, or license and collaboration agreements could negatively impact our receipt of commercial milestone payments or royalties; and
- adverse regulatory or legislative developments could 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, which may significantly reduce expected royalty revenue and commercial milestone payments and could require significant expense to address the associated legal and regulatory issues.

If the revenues generated by sales of Leqvio are lower than expected, our business could be materially adversely affected.

Geopolitical risks associated with the ongoing military conflict between Russia and Ukraine could have an adverse impact on our business, financial condition and results of operations, 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 limitations, 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 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.

We expect our operating results to fluctuate in future periods, which may adversely affect our stock price.

Our quarterly operating results have fluctuated in the past, and may continue to do so in the future. Our operating results may fluctuate due to the level of success of our commercial efforts and resulting revenues, as well as the variable nature of our operating expenses as a result of the timing and magnitude of expenditures. For example, due to the impact of the COVID-19 pandemic, combined net product revenues in the first quarter of 2022 for our commercially approved products were negatively impacted. In addition, in one or more future periods, our results of operations may fall below the expectations of securities analysts and investors. In that event, the market price of our common stock could substantially decline.

If the estimates we make, or the assumptions on which we rely, in preparing our condensed consolidated 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 management. If, for any reason, our 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 June 30, 2023, we had $2.06 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 condensed consolidated financial statements. In addition, should our investments cease paying or reduce the amount of interest paid to us, our interest income would suffer. The market risks associated with our investment portfolio may have an adverse effect on our results of operations, 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, 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 law could adversely affect our business 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, cash flow, financial condition or results of operations.

Additionally, the Organization for Economic Co-operation and Development, or 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, the 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.

Risks Related to Our Dependence on Third Parties

We may not be able to execute our business strategy if we are unable to maintain existing or enter into new alliances with other companies that can provide business and scientific capabilities and funds for the development and commercialization of our product candidates. If we are unsuccessful in forming or maintaining these alliances on terms favorable to us, our business may not succeed.

We are continuing to advance our commercial capabilities, including in marketing, sales, market access and distribution, to support our wholly-owned products. We also continue to advance our growing pipeline of RNAi therapeutic opportunities. However, we may not have adequate capacity or capabilities to advance all of our therapeutic opportunities. Accordingly, we have entered into alliances with other companies and collaborators that we believe can provide such capabilities in certain territories and/or for certain product candidates, and we intend to enter into additional such alliances in the future. Our collaboration strategy is to form alliances that create significant value for us and our collaborators in the advancement of RNAi therapeutics as a new class of innovative medicines. Specifically, with respect to our Genetic Medicine pipeline, as a result of our broad strategic alliance with Sanofi formed in 2014, Sanofi has the right to develop and commercialize fitusiran globally. In addition, we formed a collaboration with MDCO (which was acquired by Novartis in January 2020) to advance inclisiran. In March 2018, we entered into a discovery collaboration with Regeneron to identify RNAi therapeutics for NASH and potentially other related diseases, and in November 2018, we and Regeneron entered into a separate, fifty-fifty collaboration to further research, co-develop and commercialize any therapeutic product candidates that emerge from these discovery efforts. In October 2017, we announced an exclusive licensing agreement with Vir for the development and commercialization of RNAi therapeutics for infectious diseases, including chronic HBV infection. In April 2020, we entered into a development and commercialization collaboration with Dicerna (which was acquired by Novo Nordisk in December 2021) to advance investigational RNAi therapeutics for the treatment of alpha-1 liver disease. With respect to our CNS/Ocular Disease pipeline, in April 2019, we announced 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. With respect to our Cardio-Metabolic pipeline, on July 21, 2023, we entered into a Collaboration and License Agreement with Roche for the worldwide joint development of pharmaceutical products containing zilebesiran.

In such alliances, 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 alliances, we also may expect our collaborators to develop, market and/or sell certain of our product candidates. We may have limited or no control over the development, sales, marketing and distribution activities of these third parties. 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 all future 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 such collaboration referenced in clauses (i)-(iv) above, we are entitled to royalties on the sales of each of these products. If our collaborators are not successful in their development and/or commercialization efforts, our future revenues from RNAi therapeutics for these indications may be adversely affected. For example, while Leqvio was granted marketing authorization by the EC in Europe, in December 2020, Novartis received a complete response letter from the FDA stating that the agency 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 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. 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 revenues beginning in 2030.

We may not be successful in entering into future alliances on terms favorable to us due to various factors, including our ability to demonstrate improved product profiles from our new technologies, including our IKARIA and GEMINI platforms, 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 drug candidates, our ability to manufacture or have third parties manufacture RNAi therapeutics, the strength of our intellectual property and/or concerns around challenges to our intellectual property. For example, the occurrence of a fatal thrombotic serious adverse event, or SAE, in our fitusiran study in 2017 and a subsequent pause in dosing and enrollment in fitusiran clinical studies in 2020 could contribute to further concerns about the safety of specific therapeutic candidates or therapeutic candidates for specific diseases. Even when we succeed in securing such alliances, 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 or sales of an approved drug are lower than we expected.

Furthermore, any delay in entering into collaboration agreements would likely either delay the development and commercialization of certain of our product candidates and reduce their competitiveness even if they reach the market, or prevent the development of certain product candidates. Any such delay related to our collaborations could adversely affect our business.

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 Regeneron, Roche, Novartis, Vir, Dicerna and Sanofi. We may not, however, be able to enter into additional collaborations for certain other programs, and the terms of any collaboration agreement 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 our product candidates to market. If we do not have sufficient funds to develop and bring our product candidates to market, we will not be able to generate revenues from these product candidates, and this will substantially harm our business.

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 MDCO, which was acquired by Novartis in January 2020, 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 of our technology developed in the course of 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 each party's rights and obligations under 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 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 RNAi therapeutics, 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 growing manufacturing capabilities, and in order 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, contract for, 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 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 with the possibility to manufacture drug substances for late-stage clinical development and, to the extent our products are approved, commercial use, in the future.

At the present time, we can only 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 all of our finished drug products required for clinical and commercial use. There are a limited number of CMOs and we currently rely on a limited number of North American and European CMOs to manufacture our siRNA therapeutic products. 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 ultimately delay our clinical trials and potentially put at risk commercial supply, as well as result in additional expense to us. To fulfill our future requirements, we will likely need to secure 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. As noted above, in order to ensure long-term supply capabilities for our RNAi therapeutics, we are developing our own capabilities to manufacture synthetic siRNA drug substances.

In addition to the manufacture of the 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. Given our dependence on a limited number of CMOs to supply our commercial products and clinical candidates, and our growing dependence on our own facility, any delay or setback in the manufacture of our products could impede ongoing clinical and commercial supply, which could significantly impact our revenues and operating results. In addition, to the extent we or our partners 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 partners' product candidates.

The manufacturing process for our approved products and any other products 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.

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 delays in supply;
- 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 products.

We rely on third parties to conduct our clinical trials and source certain materials for our pre-clinical testing and studies, and if they 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, 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 certain 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 all of our product candidates in clinical development, and to implement timely corrective action to 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, the EMA, the PMDA in Japan or comparable 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 to adhere to our protocols or regulatory requirements or if such third parties otherwise fail to meet deadlines, our development plans and/or regulatory reviews for marketing approvals may be delayed or terminated. As a result, our stock price would likely be negatively impacted, and our results of operations and the commercial prospects for our product candidates would be harmed, our costs could increase and our ability to generate additional revenues could be delayed.

Before conducting clinical trials to demonstrate the safety and efficacy of our product candidates in humans in support of Investigational New Drug, or 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, or the PRC, and Cambodia. The supply of these non-human primates is currently constrained due to factors such as their limited worldwide availability, trade relations between the U.S. and the PRC, and heightened scrutiny of non-human primates originating from Cambodia following allegations in late 2022 that certain Cambodian businesses and government officials may have engaged in the smuggling of non-human primates. We may encounter delays in obtaining a sufficient supply of such non-human primates to enable the conduct of our pre-clinical studies. Our inability to obtain access to a sufficient supply of these non-human primates in a timely manner or at all may impair our ability to complete pre-clinical studies to support IND applications or similar applications in other jurisdictions or delay the submission of such applications.

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 of the 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 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 with which to attract and reward qualified individuals than we do. In addition, if we are not successful commercializing our approved products, we may be unable to attract and retain highly qualified sales and marketing professionals to support our approved products and our future products, if approved. Accordingly, we may be unable to attract and retain suitably qualified individuals in order 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 drugs.

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 *Alnylam P^{5}x25* 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., the 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 or the public's legitimate interests 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 business operations. The secure maintenance of this information is critical to our operations and business strategy. Some of this information could be an attractive target of 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 and consultants 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 conflict in Ukraine), 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.

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 candidates we or our partners develop may fail in development or be delayed to a point where they do 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 partnered 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.

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. 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 for which we include an open-label clinical trial when studied in a controlled environment with a placebo or active control.

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 APOLLO-B and HELIOS-B Phase 3 clinical trials of patisiran and vutrisiran, respectively, which are investigating the potential of patisiran and vutrisiran to treat the cardiac manifestations of disease in patients with ATTR amyloidosis with cardiomyopathy. We announced positive topline results from the APOLLO-B study in August 2022, and patients enrolled in the study are receiving patisiran as part of an open-label extension period. While both patisiran and vutrisiran have 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 APOLLO-B and/or HELIOS-B will support approval of patisiran and/or 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 patisiran and/or vutrisiran, could have a material adverse effect on our business and operating results. 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.

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 authorities, to suspend or terminate the 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. For example, we or our partners may experience difficulty enrolling our clinical trials, including, but not limited to, the ongoing clinical trials for fitusiran, due to the availability of existing approved treatments, as well as other investigational treatments in development. In addition, 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 are focusing our cemdisiran clinical development efforts in a different indication. Delays or difficulties in patient enrollment, including the enrollment delays in our KARDIA-1 Phase 2 monotherapy study of zilebesiran that resulted from the ongoing conflict in Ukraine, or difficulties retaining trial participants, including as a result of the availability of existing or other investigational treatments or safety concerns, including the impact of public health emergencies, can result in increased costs, longer development times or termination of a clinical trial.

Although our investigational RNAi therapeutics have been generally well-tolerated in our clinical trials to date, new safety findings may emerge. For example, in September 2017, we announced that we had temporarily suspended dosing in all ongoing fitusiran studies pending further review of a fatal thrombotic serious adverse event, or SAE, that occurred in a patient with hemophilia A without inhibitors who was receiving fitusiran in our Phase 2 open label extension, or 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. 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.

As demonstrated by the discontinuation of our revusiran program in October 2016, the temporary suspension of dosing in September 2017 in our fitusiran studies, as well as Sanofi's voluntary pause of fitusiran studies in October 2020, the occurrence of SAEs and/or AEs can result in the suspension or termination of clinical trials of a product candidate by us, our partners, or the FDA or a foreign regulatory authority. 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.

Clinical trials also require the review, oversight and approval of IRBs, or, outside of the U.S., an independent ethics committee, 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 investigation 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 we develop may encounter problems during clinical trials that will cause us, an IRB, ethics committee or regulatory authorities to delay, suspend or terminate these trials, or that will delay or confound the analysis of data from these trials. If we experience any such problems, we may not have the financial resources to continue development of the product candidate that is affected, or development of any of our other product candidates. We may also lose, or be unable to enter into, collaborative arrangements for the affected product candidate and for other product candidates we are developing.

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 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 we expect 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 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 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 the 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 participants in our clinical trials or by individuals using drugs similar to our 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 partners may be unable to obtain U.S. or foreign regulatory approval for our or our partnered product candidates and, as a result, we or our partners may be unable to commercialize such product candidates.

Our and our partnered 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 partners are developing will not obtain the regulatory approvals necessary for us or our collaborators to begin selling them, or, in the case of patisiran and vutrisiran, will not obtain regulatory approval to be sold for broader indications than are 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, including patisiran, while positive, is not sufficient to support the approval of an application for regulatory approval. In February 2023, the FDA accepted our sNDA for ONPATTRO for filing and set an action date of October 8, 2023, under the PDUFA. The FDA also indicated in the sNDA filing communication letter that it is planning to hold an advisory committee meeting to discuss the application, and in July 2023, the FDA announced that an advisory committee meeting has been scheduled for September 13, 2023 to review the sNDA. Even though the sNDA has been accepted for filing, we may receive a complete response letter rather than approval, including for reasons that may be identified during the meeting of the advisory committee.

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 predictably or uniformly and can change. 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 partners 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 drugs we or our partners 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 partners may submit. Moreover, the FDA may respond to these submissions by defining requirements we or our partners may not have anticipated. Such responses could lead to significant delays and increased costs in the development of our or our partnered product candidates. In addition, because there may be approved treatments for some of the diseases for which we or our partners may seek approval, including patisiran and vutrisiran for the treatment of ATTR amyloidosis with cardiomyopathy, or treatments in development which are approved by the time we or they apply 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, if any, are not only safe and effective, but safer or more effective than existing 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 partnered 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 complete response letter 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 (which is the trade name under which inclisiran is marketed in the U.S.) in December 2021. The 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 agency could have a material adverse effect on our efforts to obtain regulatory approval for our product candidates, which could have a material adverse effect on our financial results. For instance, the FDA may request additional clinical or other data or information in connection with the regulatory review of our or our partners' product candidates, including patisiran, including by issuing a complete response letter which may require that we or our partners' submit additional clinical or other data or impose other conditions that must be met in order to secure final approval of our or our partners' 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 partnered product candidates could have a material adverse effect on our ability to generate revenues from any product candidate for which we or our partners may seek approval in the future. Furthermore, any regulatory approval to market any product, including patisiran, may be subject to limitations on the approved uses for which we or our partners 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 results of operations 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 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 partners 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 the product 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 regulatory authorities outside the U.S. and vice versa.

Even if we or our partners obtain regulatory approvals, our marketed drugs will be subject to ongoing regulatory oversight. If we or our partners 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 our business would be seriously harmed.

Following any initial regulatory approval of drugs we or our partners may develop, including our four approved drugs, we will also 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 would include results from any post-marketing tests or surveillance to monitor the safety and efficacy of our approved drugs or other drug products required as a condition of approval or 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 other product candidates may also be subject to limitations on the approved uses for which the product may be marketed, including any expanded label for ONPATTRO or 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 drug 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 drug. 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 more modest 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
- government investigations or lawsuits, including class action suits, may be brought against us.

Any of the above occurrences could reduce or prevent 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 facilities or our CMOs, or our or their 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 drug 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. We have developed cGMP capabilities and processes for the manufacture of patisiran formulated bulk drug product for commercial use. In addition, in 2020, we 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 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 may seek to market our products, we or they may be subject to, among other things, fines, 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 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 off-label information in the promotion of drug products that is not consistent with the approved labeling for those products. For example, we may not promote ONPATTRO or AMVUTTRA in the U.S. for use in any indications other than the treatment of the polyneuropathy of hATTR amyloidosis 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. For example, in April 2021, we received a subpoena from the U.S. Department of Justice, U.S. Attorney's Office for the District of Massachusetts, requiring production of documents pertaining to our marketing and promotion of ONPATTRO (patisiran) in the U.S. We responded to the subpoena and cooperated with the U.S. Attorney's Office's requests. On August 1, 2023, the U.S. Attorney's Office informed us that it planned to close its investigation into this matter. 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, financial condition or divert financial and management resources from our core business, and would have a material adverse effect on our business, financial condition and results of operations. 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 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 above, 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 receive regulatory approval to market our product candidates, the market may not be receptive to our product candidates upon their commercial introduction, which could prevent us from becoming profitable.

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 product, or to provide favorable reimbursement.

Other factors that we believe will materially affect market acceptance of our product candidates 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 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 product candidates we develop are intended to treat and the relative risks, benefits and costs of those treatments.

For example, one of our two commercially approved therapeutics for the treatment of the polyneuropathy of hATTR amyloidosis in adults, ONPATTRO, utilizes an intravenous mode of administration with pre-medication that physicians and/or patients may not readily adopt, or which may not compete favorably with other available options, 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 patients and their caregivers. Patisiran, 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. Even if we successfully scale our commercial capabilities, the market may not be receptive to our commercial products.

Having received our first product approval in August 2018, we have established our 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 several of our late-stage 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, 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 where we may retain certain product 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, AHP and PH1 are small and have not been established with precision. If the actual number of patients is smaller than we estimate, or if we cannot raise awareness of these diseases and diagnosis is not improved, our revenue and ability to achieve profitability from these products 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 results of operations and financial condition. For example, the initial indication approved by the FDA for ONPATTRO is for the treatment of the polyneuropathy of hATTR amyloidosis and not for the treatment of cardiomyopathy or other manifestations of the disease. In addition, the U.S. label does not include cardiac data included in our APOLLO-B Phase 3 study results. This had an adverse impact on the market opportunity for ONPATTRO in the U.S. While data from the APOLLO-B study of patisiran in ATTR amyloidosis patients with cardiomyopathy was positive, the Cardiovascular and Renal Drugs Advisory Committee of the FDA could determine that our data are insufficient to provide a positive recommendation for approval of our sNDA to the FDA, and later the FDA may determine that the data is not supportive of a label expansion of ONPATTRO for the treatment of cardiomyopathy, which would further impact ONPATTRO's market opportunity. In addition, our efforts to raise disease awareness and improve diagnosis of our relevant disease states were impacted by the COVID-19 pandemic. For example, in 2020 and 2021, we saw a reduction in peer to peer educational opportunities, reduced physician attendance at congresses and symposia and overall opportunities for physician engagement. As is the case with most orphan diseases, if we are unable to successfully raise awareness of these diseases and improve diagnosis, it will be more difficult or impossible to achieve profitability.

Any drugs we develop may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, thereby harming our business.

The regulations that govern marketing approvals, pricing and reimbursement for new drugs vary widely from country to country. 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 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 other programs move through late stages of development. However, a number of our programs are currently in the earlier stages of development, and we will not be able to assess the impact of price regulations for such 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 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.

Our ability to commercialize our approved products or any future products successfully also will depend in part on the extent to which reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers and other organizations. One or more of our approved products and other products for which we are able to obtain marketing approval may not be considered 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. 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 clinical trials, and the agreements are structured to link the performance of our approved products in real-world use to financial terms. Partnering with payers on these agreements is also intended to provide more certainty to them for their investment 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 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 3.0% 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.

Some of the drugs we market need to be administered under the supervision of a physician or other healthcare professional on an outpatient basis, including ONPATTRO, AMVUTTRA, GIVLAARI and OXLUMO. Under currently applicable U.S. law, certain drugs that are not usually self-administered (including injectable drugs) may be eligible for coverage under the Medicare Part B program if:

- they are incident to a physician’s services;

- they are reasonable and necessary for the diagnosis or treatment of the illness or injury for which they are administered according to accepted standards of medical practice; and
- they have been approved by the FDA and meet other requirements of the statute.

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 drug. 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 payments allowed for lower-cost drugs that are already reimbursed, may be incorporated into existing payments for other services and may reflect budgetary constraints or imperfections in Medicare 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.

President Biden signed an Executive Order on July 9, 2021 affirming the administration's policy to (i) support legislative reforms that would lower the prices of prescription drugs, including by allowing Medicare to negotiate drug prices, by imposing inflation caps, and, by supporting the development and market entry of lower-cost generic drugs and biosimilars; and (ii) support the enactment of a public health insurance option. Among other things, the Executive Order also directs the U.S. Department of Health and Human Services, or HHS, to provide a report on actions to combat excessive pricing of prescription drugs, continue to clarify and improve the approval framework for generic drugs and identify and address any efforts to impede generic drug competition, enhance the domestic drug supply chain, reduce the price that the Federal government pays for drugs, and address price gouging in the industry; and directs the FDA to work with states and Indian Tribes that propose to develop section 804 Importation Programs in accordance with the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, and the FDA's implementing regulations. The FDA released such implementing regulations on September 24, 2020, which went into effect on November 30, 2020, providing guidance for states to build and submit importation plans for drugs from Canada. In response, authorities in Canada have passed rules designed to safeguard the Canadian drug supply from shortages. If implemented, 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. Further, on November 20, 2020, the Centers for Medicare and Medicaid Services, or CMS, issued an Interim Final Rule implementing the MFN Model under which Medicare Part B reimbursement rates will be calculated for certain drugs based on the lowest price drug manufacturers receive in OECD countries with a similar gross domestic product per capita. The MFN Model regulations mandate participation by identified Part B providers and would have applied to all U.S. states and territories for a seven-year period beginning January 1, 2021, and ending December 31, 2027. However, on December 29, 2021, CMS rescinded the proposed MFN rule. Additionally, on December 2, 2020, HHS published a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. Pursuant to court order, the removal and addition of the aforementioned safe harbors have been delayed until January 1, 2023, requiring manufacturers to ensure the full value of co-pay assistance is passed on to the patient or these dollars will count toward the Average Manufacturer Price and Best Price calculation of the drug. On May 17, 2022, the U.S. District Court for the District of Columbia granted the Pharmaceutical Research and Manufacturers of America's motion for summary judgement invalidating the accumulator adjustment rule. 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 legislative measures to control drug costs.

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 government has continued to focus on legislative and regulatory changes designed to control costs. Specifically, there have been several recent U.S. Congressional inquiries and proposed federal and state legislation 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.

A number of other legislative and regulatory changes in the healthcare system in the U.S. and other major healthcare markets have been proposed or enacted in recent months and years, and such efforts have expanded substantially in recent years. These developments could, directly or indirectly, affect our ability to sell ONPATTRO, AMVUTTRA, GIVLAARI, OXLUMO or future products, if approved, at a favorable price.

In particular, in March 2010, the Patient Protection and Affordable Care Act, also referred to as the Affordable Care Act, or the ACA, was signed into law. This legislation changed the system of healthcare insurance and benefits intended to broaden coverage and control costs. The law also contains provisions that affect companies in the pharmaceutical industry and other healthcare related industries by imposing additional costs and changes to business practices. Among the provisions affecting pharmaceutical companies are the following:

- Mandatory rebates for drugs sold into the Medicaid program were increased, and the rebate requirement was extended to drugs used in risk-based Medicaid managed care plans.
- The 340B Drug Pricing Program under the Public Health Service Act was extended to require mandatory discounts for drug products sold to certain critical access hospitals, cancer hospitals and other covered entities.
- Pharmaceutical companies are required to offer discounts on brand-name drugs to patients who fall within the Medicare Part D coverage gap, commonly referred to as the “donut hole.”
- Pharmaceutical companies are required to pay an annual non-tax deductible fee to the federal government based on each company’s market share of prior year total sales of branded products to certain federal healthcare programs, such as Medicare, Medicaid, Department of Veterans Affairs and Department of Defense. Since we expect our branded pharmaceutical sales to constitute a small portion of the total federal healthcare program pharmaceutical market, we do not expect this annual assessment to have a material impact on our financial condition.
- The law provides that approval of an application for a follow-on biologic product may not become effective until 12 years after the date on which the reference innovator biologic product was first licensed by the FDA, with a possible six-month extension for pediatric products. After this exclusivity ends, it will be easier for generic manufacturers to enter the market, which is likely to reduce the pricing for such products and could affect our profitability.
- The law creates a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected.
- The law expands eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer’s Medicaid rebate liability.
- The law expands the entities eligible for discounts under the Public Health Service Act pharmaceutical pricing program.
- The law expands healthcare fraud and abuse laws, including the civil FCA and the federal Anti-Kickback Statute, new government investigative powers, and enhanced penalties for noncompliance.
- The law establishes new requirements to report financial arrangements with physicians and teaching hospitals and to annually report drug samples that manufacturers and distributors provide to physicians.
- The law establishes a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.
- The law established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery methods.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation’s automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of 2% per fiscal year. These reductions went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2030, with the exception of a temporary suspension from May 1, 2020 through March 31, 2022 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.

Further, there have been several changes to the 340B Drug Pricing Program, which imposes ceilings on prices that drug manufacturers can charge for medications sold to certain healthcare facilities. On December 27, 2018, the District Court for the District of Columbia invalidated a reimbursement formula change under the 340B Drug Pricing Program, and CMS subsequently altered the fiscal years 2019 and 2018 reimbursement formula on specified covered outpatient drugs. The court ruled this change was not an “adjustment” which was within the Secretary’s discretion to make but was instead a fundamental

change in the reimbursement calculation. However, most recently, on July 31, 2020, the U.S. Court of Appeals for the District of Columbia Circuit overturned the district court's decision and found that the changes were within the Secretary's authority. On September 14, 2020, the plaintiffs-appellees filed a Petition for Rehearing En Banc (i.e., before the full court), and the court denied this petition on October 16, 2020. Plaintiffs-appellees filed a petition for a writ of certiorari at the Supreme Court on February 10, 2021. On July 2, 2021, the Supreme Court granted the petition. On June 15, 2022, the Supreme Court unanimously reversed the Court of Appeals' decision, holding that HHS's 2018 and 2019 reimbursement rates for 340B hospitals were contrary to the statute and unlawful. It is unclear how these developments could affect covered hospitals who might purchase our future products and affect the rates we may charge such facilities for our approved products in the future, if any.

The Inflation Reduction Act of 2022, or IRA, which among other things, allows for CMS to negotiate prices for certain single-source drugs and biologics reimbursed under Medicare Part B and Part D, beginning with ten high-cost drugs paid for by Medicare Part D starting in 2026, followed by 15 Part D drugs in 2027, 15 Part B or Part D drugs in 2028, and 20 Part B or Part D drugs in 2029 and beyond. The legislation subjects drug manufacturers to civil monetary penalties and a potential excise tax for failing to comply with the legislation by offering a price that is not equal to or less than the negotiated "maximum fair price" under the law or for taking price increases that exceed inflation. The legislation also requires manufacturers to pay rebates for drugs in Medicare Part D whose price increases exceed inflation. Further, the legislation caps Medicare beneficiaries' annual out-of-pocket drug expenses at $2,000. Under the IRA, a second FDA approval for vutrisiran for Stargardt Disease would cause us to lose the single-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 in Stargardt Disease. 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 full effects of the U.S. healthcare reform legislation cannot be known until the law is fully implemented through regulations or guidance issued by CMS and other federal and state healthcare agencies. The financial impact of the U.S. healthcare reform legislation over the next few years will depend on a number of factors, including, but not limited, to the policies reflected in implementing regulations and guidance, and changes in sales volumes for products affected by the new system of rebates, discounts and fees. This legislation may also have a positive impact on our future net sales, if any, by increasing the aggregate number of persons with healthcare coverage in the U.S.

Since its enactment, there have been numerous judicial, administrative, executive, and legislative challenges to certain aspects of the ACA, and we expect there will be additional challenges and amendments to the ACA in the future. On June 17, 2021, the U.S. Supreme Court dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the ACA. Prior to the Supreme Court's decision, President Biden issued an executive order to initiate a special enrollment period from February 15, 2021 through August 15, 2021 for the purpose of obtaining health insurance coverage through the ACA marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. It is unclear how other healthcare reform measures of the Biden administration or other efforts, if any, to challenge, repeal or replace the ACA will impact our business.

At the state level, legislatures have become increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical product pricing. Some of these measures include price or patient reimbursement constraints, discounts, restrictions on certain product access, marketing cost disclosure and transparency measures, and, in some cases, measures designed to encourage importation from other countries and bulk purchasing. 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. Further federal and state 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 an adverse effect on 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 overall financial condition and ability to develop drug candidates.

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, the 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, and other state and national anti-bribery and anti-money laundering laws in the countries in which we conduct activities. Anti-corruption laws are interpreted broadly and prohibit companies and their employees, agents, contractors, and other collaborators from authorizing, promising, offering, or providing, directly or indirectly, improper payments or anything else of value to recipients in the public or private sector. 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 our employees, agents, contractors, and other collaborators, 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 civil and criminal fines and penalties, imprisonment, the loss of export or import privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm, and other consequences.

We remain focused on these laws and the activities they regulate and, as detailed above, 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. 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 is 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, there can be considerable pressure by governments and other stakeholders 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. In some countries, we may be required to conduct a clinical study or other studies that compare the cost-effectiveness of a product candidate to other available therapies in order to obtain or maintain reimbursement or pricing approval, which is time-consuming and costly. We cannot be sure that such prices and reimbursement will be acceptable to us or our strategic partners. 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 strategic partners and the potential profitability of our approved products or any future products in those countries would be negatively affected. Another impact from the tightening pricing control could be felt from greater competition from less expensive generic or biosimilar products once the exclusivity expires; the governments have adopted policies to switch prescribed products to generic versions in order to cut the medical cost.

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 affect our ability to develop, market and sell our products and may harm our reputation.

As a manufacturer of pharmaceuticals, we are subject to federal, state, and comparable foreign healthcare laws and regulations pertaining to fraud and abuse and patients' rights, in addition to legal obligations related to privacy, data protection and information security. These laws and regulations include:

- 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 for each violation, plus up to three times the remuneration involved, 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.

- The federal civil monetary penalties laws, which impose civil fines for, among other things, the offering or transfer of remuneration to a Medicare or state healthcare program beneficiary if the person knows or should know it is likely to influence the beneficiary's selection of a particular provider, practitioner, or supplier of services reimbursable by Medicare or a state healthcare program, unless an exception applies.
- The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created 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 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 relating to healthcare matters. 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, which imposes 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 ACA 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 HHS 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 required information may result in civil monetary penalties for all payments, transfers of value or ownership or investment interests that are not timely, accurately, and completely reported in an annual submission.
- 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 product 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 and other territories. Failure to comply with our obligations under the privacy regime could expose us to significant fines and/or adverse publicity, which could have material adverse effects on our reputation and business.
- The California Consumer Privacy Act of 2018, or CCPA, effective as of January 1, 2020, that gives California residents expanded rights to access and require deletion of their personal information, opt out of certain personal information sharing, and receive detailed information about how their personal information is used. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that is expected to increase data breach litigation.
- Additionally, a new California ballot initiative, the California Privacy Rights Act of 2020, or CPRA, was passed in November 2020. Effective as of January 1, 2023, the CPRA imposes additional obligations on companies covered by the legislation and will significantly modify the CCPA, including by expanding consumers' rights with respect to

certain sensitive personal information. The CPRA also creates a new state agency that will be vested with authority to implement and enforce the CCPA and the CPRA. Furthermore, similar laws were enacted in four other states and proposed in numerous others. The effects of the CCPA and the CPRA 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 provides 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 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, loss of eligibility to obtain approvals from the FDA, 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, any of which could adversely affect our financial results. 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 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 other 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:

- adverse regulatory inspection findings;
- untitled letters or warning letters;
- voluntary or mandatory product recalls or public notification or medical product safety alerts to healthcare professionals;
- restrictions on, or prohibitions against, marketing our products;
- restrictions on, or prohibitions against, importation or exportation of our products;
- suspension of review or refusal to approve pending applications or supplements to approved applications;
- exclusion from participation in government-funded healthcare programs;
- exclusion from eligibility for the award of government contracts for our products;
- suspension or withdrawal of product approvals;
- product seizures;
- injunctions; and
- civil and criminal penalties, up to and including criminal prosecution resulting in fines, exclusion from healthcare reimbursement programs and imprisonment.

Moreover, federal, state or foreign laws or regulations are subject to change, and while we, our collaborators, CMOs and/or service providers currently may be compliant, that could change 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 some 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 out of government claims challenging the legality of their patient assistance programs under a variety of federal and state laws. It is possible that we may make grants to independent charitable foundations that help financially needy patients with their premium, co-pay, and co-insurance obligations. If we choose to do so, and if we or our vendors or donation recipients are deemed to fail to comply with relevant laws, regulations or evolving government guidance in the operation of these programs, we could be subject to damages, fines, penalties, or other criminal, civil, or administrative sanctions or enforcement actions. We cannot ensure that our compliance controls, policies, and procedures will be sufficient to protect against acts of our employees, business partners, or vendors that may violate the laws or regulations of the jurisdictions in which we operate. Regardless of whether we have complied with the law, a government investigation could impact our business practices, harm our reputation, divert the attention of management, increase our expenses, and reduce the availability of foundation support for our patients who need assistance.

We are subject to governmental regulation and other legal obligations, particularly 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 put in place a number of measures to ensure compliance with the data protection regime. The GDPR requires us to inform data subjects of how we process their personal data and how they can exercise their rights, ensure we have a valid legal basis to process personal data (if this is consent, the requirements for obtaining consent carries a higher threshold), appoint a data protection officer where sensitive personal data (i.e., health data) is processed on a large scale, introduces mandatory data breach notification requirements throughout the EEA and UK, requires us to maintain records of our processing activities and to document data protection impact assessments where there is high risk processing, imposes additional obligations on us when we are contracting with service providers, requires appropriate technical and organisational measures to be put in place to safeguard personal data and 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 Maximillian 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 also 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 trials and may adversely affect our business and financial position. 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 all 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 the adequacy decision.

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, so that 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.

We are subject to the supervision of local data protection authorities in those jurisdictions where 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 they are 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 new regulations will be adopted.

Compliance with U.S. and international data protection laws and regulations could require us to take on more onerous obligations in our contracts, restrict our ability to collect, use and disclose data, or in some cases, impact 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 financial position, results of operations and cash flows.

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 CARES Act, as well as subsequent legislation, these reductions were suspended from May 1, 2020 through December 31, 2021 due to the COVID-19 pandemic. The full impact on our business of these automatic cuts is uncertain.

If other federal spending is reduced, any budgetary shortfalls may also impact the ability of relevant agencies, such as the FDA or the National Institutes of Health to continue to function. 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. Further, there has been heightened governmental scrutiny recently over the manner in which drug manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products.

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.

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. Following the decision to discontinue clinical development of revusiran, we conducted a comprehensive evaluation of available revusiran data. We reported the results of this evaluation in August 2017, however, our investigation did not result in a conclusive explanation regarding the cause of the mortality imbalance observed in the ENDEAVOUR Phase 3 study. In addition, in September 2017, we announced that we had temporarily suspended dosing in all ongoing fitusiran studies pending further review of a fatal thrombotic SAE and agreement with regulatory authorities on a risk mitigation strategy. Notwithstanding the risks undertaken by all persons who participate in clinical trials, and the information on risks provided to study investigators and patients participating in our clinical trials, including the revusiran and fitusiran studies, it is possible that product liability claims will be asserted against us relating to the worsening of a patient's condition, injury or death alleged to have been caused by one of our product candidates, including revusiran or fitusiran. 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.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with governmental regulations, comply with 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. 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 and results of operations, 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 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 licensees may be required to obtain licenses under third-party patents to market one or more of our or our partner's approved products, or further develop and commercialize future products, or continue to develop candidates in our pipeline being developed by us or our licensees. 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 during certain collaborations. The process of obtaining patent protection is expensive and time-consuming. If 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 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 Congress of the United States 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 and financial condition could be materially adversely affected.

Failure to obtain and maintain all available regulatory exclusivities, broad patent scope and to maximize patent term restoration or extension on patents covering our products may lead to loss of exclusivity and early 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 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 Biopharma Corp., or 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 to which we are 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. 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: 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 *inter partes* and post-grant review proceedings introduced by provisions of the AIA, which became available to third party challengers on September 16, 2012, 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 compositions and methods of ANGPTL3, arguing that the granted claims are invalid. An oral hearing was held at the EPO in February 2021, where the patent was revoked. A notice of appeal of the EPO's decision was filed in June 2021. 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. An oral hearing is anticipated at a time to be determined by the EPO. 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 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 and 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 licensees, 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 licensees. 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 and/or a court rules that we need such patent rights that have been asserted against us and we are not able to obtain a license on reasonable terms, we may be unable to market products, including ONPATTRO, AMVUTTRA, GIVLAARI

or OXLUMO, or 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 are 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 as well. During the pendency of this litigation, as well as the Dicerna litigation described above, 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. We and Dicerna settled the ongoing litigation between us in April 2018. In March 2022, we announced that we separately filed suit in United States District Court for the District of Delaware against Pfizer and Moderna, Inc., seeking damages for infringement of U.S. Patent No. 11,246,933 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. The court combined the two patents in a single suit for each of Pfizer/BioNTech and Moderna with trial dates set for each in November 2024. On May 26, 2023, we filed new 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 recently granted 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. The most recently filed lawsuits are pending before the court with no trial date set. 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 the ongoing 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 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. Any license required under any patent may not be made available on commercially reasonable terms, if at all. In addition, such licenses are likely to be non-exclusive and,

therefore, our competitors may have access to the same technology 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 any other product candidates that we develop, or we could lose certain rights to grant sublicenses.

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 amendment 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 rejecting 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-judgement 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, 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, others 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 competitive business position.

Risks Related to Competition

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

- much greater financial, technical and human resources than we have at every stage of the discovery, development, manufacture and commercialization of products;
- 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;
- 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. For example, if approved by the FDA, patisiran, our RNAi therapeutic in development for ATTR amyloidosis patients with cardiomyopathy, would compete with tafamidis, marketed by Pfizer, which is currently approved to treat this disease. We also expect to face competition from new drugs that enter the market. There are a number of drugs currently under development, which 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, or marketed and sold more effectively, than any products we develop and commercialize. For example, we developed ONPATTRO and AMVUTTRA for the treatment of hATTR amyloidosis. In August 2018, the FDA approved ONPATTRO lipid complex injection for the treatment of the polyneuropathy of hATTR amyloidosis in adults, and the EC granted marketing authorization for ONPATTRO for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy. We are aware of other approved products used to treat this disease, including tafamidis, and inotersen, developed and marketed by Ionis, as well as product candidates in various stages of clinical development, including eplontersen, an additional investigational drug developed by Ionis in partnership with AstraZeneca, which met co-primary and secondary endpoints in a Phase 3 study for the polyneuropathy of hATTR amyloidosis, and is currently under regulatory review by the FDA with a PDUFA action date of December 22, 2023. Finally, BridgeBio Pharma, Inc., or BridgeBio, announced positive results from its Phase 3 clinical trial of acoramidis, a TTR stabilizer, in ATTR-CM in July 2023, and noted that they anticipate filing an NDA with the FDA by the end of 2023. 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. Moreover, positive or negative data and/or the commercial success or failure of competitive products could negatively impact our stock price. For example, our stock price was negatively impacted by the results of Part A of BridgeBio's Phase 3 clinical trial.

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

- the safety and effectiveness of our products relative to alternative therapies, if any;
- the ease with which our 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 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 Oxabact®, a bacteria-based investigational therapy in development by OxThera AB, reloxaliase an investigational enzyme therapy in Phase 3 development for primary or severe secondary hyperoxaluria by Allena Pharmaceuticals, Inc., and nedosiran, an investigational RNAi therapeutic in development by Dicerna for the treatment of primary hyperoxaluria. In July 2019, the FDA granted a Breakthrough Therapy Designation to nedosiran for the treatment of patients with primary hyperoxaluria, and in August 2021, Dicerna reported positive topline results from its PHYOX2 pivotal clinical trial of nedosiran for the treatment of primary hyperoxaluria. Based on the results of the trial, Novo Nordisk submitted an NDA to the FDA in September 2022 for the treatment of PH1 in patients aged six years and older. 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 product candidate. Our competitors may develop or commercialize products with significant advantages over any products we develop based on any of the factors listed above or on other factors. In addition, our competitors may develop strategic alliances with or receive funding from larger pharmaceutical or biotechnology companies, providing them with an advantage over us. Our competitors may therefore be more successful in commercializing their products than we are, which could adversely affect our competitive position and business. Competitive products may make any products we 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 the ability to execute on our business plan. Furthermore, we 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 are targeting could make our product candidates noncompetitive, obsolete or uneconomical.

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

In addition to the competition we face from competing drugs in general, we 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 not with synthetic siRNAs but 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, Takeda Pharmaceutical Company Ltd., or Takeda, Marina Biotech, Inc., Arrowhead Pharmaceuticals Inc, Inc., or Arrowhead, Quark Pharmaceuticals, Inc., or Quark, Silence, Arbutus, Sylentis, S.A.U, or Sylentis, Dicerna and its collaborators, WAVE Life Sciences Ltd., Arcturus Therapeutics Inc., and Genevant Sciences, launched by Arbutus and Roivant Sciences. In addition, we granted licenses or options for licenses to Ionis, Benitec Biopharma Ltd., or Benitec, Arrowhead, Arbutus, Quark, Sylentis and others 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 us.

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 also compete with companies working to develop antisense-based drugs. Like RNAi therapeutics, antisense drugs target mRNAs in order to suppress the activity of specific genes. Akcea Therapeutics, Inc. (acquired by Ionis in October 2020), has received marketing approval for an antisense drug, inotersen that was developed by Ionis, for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR amyloidosis. 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. Safe and effective means to deliver siRNAs to the relevant cell and tissue types may be developed by our competitors, and our ability to successfully commercialize a competitive product would be adversely affected. In addition, substantial resources are being expended by third parties in the effort to discover and develop a safe and effective means of delivering siRNAs into the relevant cell and tissue types, both in academic laboratories and in the corporate sector. Some of our competitors have substantially greater resources than we do, and if our competitors are able to negotiate exclusive access to those delivery solutions developed by third parties, we may be unable to successfully commercialize our product candidates.

Risks Related to Our Common Stock

If our stock price fluctuates, purchasers of our common stock could incur substantial losses.

The market price of our common stock has fluctuated significantly and may continue to fluctuate significantly in response to factors that are beyond our control. The stock market in general has from time to time experienced extreme price and volume fluctuations, and the biotechnology sector in particular has experienced extreme price and volume fluctuations. The market prices of securities of pharmaceutical and biotechnology companies have been extremely volatile, and have experienced fluctuations that often have been unrelated or disproportionate to the clinical development progress or operating performance of these companies, including as a result of adverse development events reported by other companies, and more recently as a result of disruptions to the U.S. banking system caused by the failure of Silicon Valley Bank. For example, the trading price for our common stock and the common stock of other biopharmaceutical companies was highly volatile during the initial stages of the COVID-19 pandemic. These broad market and sector fluctuations have resulted and could in the future result in extreme fluctuations in the price of our common stock, which could cause purchasers of our common stock to incur substantial losses.

We may incur significant costs from class action litigation.

Our stock price may fluctuate for many reasons, including as a result of public announcements regarding the progress of our development and commercialization efforts or the development and commercialization efforts of our collaborators and/or competitors, the addition or departure of our key personnel, variations in our quarterly operating results and changes in market valuations of pharmaceutical and biotechnology companies. When the market price of a stock has been volatile as our stock price has been, holders of that stock have occasionally brought securities class action litigation against the company that issued the stock.

For example, on September 12, 2019, the Chester County Employees Retirement Fund, individually and on behalf of all others similarly situated, filed a purported securities class action complaint alleging violation of federal securities laws against us, certain of our current and former directors and officers, and the underwriters of our November 14, 2017 public stock

offering, in the Supreme Court of the State of New York, New York County. While we believe the allegations in the New York State Securities Litigation were without merit, in August 2021, the parties reached an agreement in principle to resolve the matter. At a hearing on April 12, 2022, the Supreme Court of the State of New York granted final approval to the settlement. Proceedings in the First Department were adjourned until April 2022, pending final approval of any settlement, and were withdrawn as a result of final approval on April 18, 2022. Future litigation could result in substantial costs and divert our management's attention and resources, which could cause serious harm to our business, 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 in connection with certain litigation, and such obligations are not covered by insurance.

Future sales of shares of our common stock, including by our significant stockholders, us or our directors and officers, 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 June 30, 2023, our seven largest stockholders beneficially owned in excess of 50% of our outstanding shares of common stock. If our significant stockholders, or we or our officers and directors, 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.

Regeneron's ownership of our common stock could delay or prevent a change in corporate control.

As of May 21, 2019, the closing date of the stock purchase in connection with the 2019 Regeneron collaboration, Regeneron held approximately 4% of our outstanding common stock and has the right to increase its ownership up to 30%. This concentration of ownership could harm the market price of our common stock in the future by:

- delaying, deferring or preventing a change in control of our company;
- impeding a merger, consolidation, takeover or other business combination involving our company; or
- discouraging a potential acquirer from making a tender offer or otherwise attempting to obtain control of our company.

Anti-takeover provisions in our charter 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.

Provisions in our certificate of incorporation and our bylaws may delay or prevent an acquisition of us or a change in our management. In addition, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Because our board of directors is responsible for appointing the members of our management team, these provisions could in turn affect any attempt by our stockholders to replace current members of our management team. These provisions include:

- a classified board of directors;
- a prohibition on actions by our stockholders by written consent;
- limitations on the removal of directors; and
- 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.

Risks Related to Our Convertible Notes

Servicing our debt may require a significant amount of cash. We may not have sufficient cash flow from our business to pay our indebtedness.

On September 12, 2022, we commenced a private offering of $900.0 million in aggregate principal amount of 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 the Additional Notes, bringing the total aggregate principal amount of the Notes to $1.04 billion. 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, any of our future debt agreements may contain restrictive covenants that may prohibit us from adopting any of these alternatives. Our failure to comply with these covenants could result in an event of default which, if not cured or waived, could result in the acceleration of our debt.

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, and our future debt may contain limitations on our ability to pay cash upon conversion of the Notes or to repurchase the Notes.

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.

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, results of operations 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.

The conditional conversion feature of the Notes, if triggered, may adversely affect our financial condition and operating results.

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 our 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. Our Notes may become in the future convertible at the option of their holders under certain circumstances. If holders of our 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 will be 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 will be treated as a debt discount for accounting purposes, which will be 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, we expect that the shares of common stock underlying the Notes will be reflected in our diluted earnings per share using the “if converted” method, in accordance with ASU 2020-06. Under that method, diluted earnings per share would generally be 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 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 June 30, 2023, 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.

Tolga Tanguler, Chief Commercial Officer

On May 18, 2023, Tolga Tanguler, our Chief Commercial Officer, entered into a Rule 10b5-1 trading plan that provides that Mr. Tanguler, acting through a broker, may sell up to an aggregate of 20,024 shares of our common stock received upon the settlement of awards granted to Mr. Tanguler 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 August 16, 2023 to May 10, 2024. The plan is scheduled to terminate on May 10, 2024, subject to earlier termination upon the sale of all shares subject to the plan, upon termination by Mr. Tanguler or the broker, or as otherwise provided in the plan.

Phillip A. Sharp, Ph.D., Director

On May 16, 2023, Phillip A. Sharp, Ph.D., a member of our board of directors, entered into a Rule 10b5-1 trading plan that provides that Dr. Sharp, acting through a broker, may sell up to an aggregate of 63,750 shares of our common stock received upon the exercise of options granted to Dr. Sharp 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 September 1, 2023 to June 3, 2024. The plan is scheduled to terminate on June 3, 2024, subject to earlier termination upon the sale of all shares subject to the plan upon termination by Dr. Sharp or the broker, or as otherwise provided in the plan.

ITEM 6. EXHIBITS

10.1#†*	Amendment No. 1 entered into as of April 10, 2023 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.
*	Management contracts or compensatory plans or arrangements.
+	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: August 3, 2023

/s/ Yvonne L. Greenstreet, MBChB, MBA

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

Date: August 3, 2023

/s/ Jeffrey V. Poulton

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

Exhibit 10.1

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. 1
to the Master Agreement

This Amendment No. 1 ("**Amendment No. 1**") to the Master Agreement is entered into and effective as of April 10, 2023 ("**Amendment No. 1 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 Master Agreement dated April 8, 2019 (the "**Agreement**");

WHEREAS, Regeneron and Alnylam find it in their respective interests to amend the Agreement to clarify certain terms;

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. **Defined Terms.** The following defined terms in Article 1 of the Agreement are hereby restated and amended, effective as of the Effective Date of the Agreement:

1.12 "**Alnylam Background Technology**" means (a) on a Program-by-Program basis, (i) Information that is necessary or reasonably useful to Exploit any Collaboration Product under such Program and (ii) Patent Rights that Cover any Collaboration Product under such Program or the Exploitation of any Collaboration Product under such Program, and (b) Information or Patent Rights that are necessary or reasonably useful to perform any Technology Development Activities, in each case, ((a) and (b)), that are Controlled by Alnylam or its Affiliates as of the Execution Date or at any time thereafter until the end of the Term, but excluding Alnylam Collaboration IP and Alnylam's interest in the Joint Collaboration IP.

1.218 "**Regeneron Background Technology**" means (a) on a Program-by-Program basis, (i) Information that is necessary or reasonably useful to Exploit any Collaboration Product under such Program and (ii) Patent Rights that Cover any Collaboration Product under such Program or the Exploitation of any Collaboration Product under such Program; and (b) Information or Patent Rights that are necessary or reasonably useful to perform any Technology Development Activities, in each case, ((a) and (b)), that are Controlled by Regeneron or its Affiliates as of the Execution Date or at any time thereafter until the end of the Term, but excluding Regeneron Collaboration IP and Regeneron's interest in the Joint Collaboration IP. Notwithstanding the foregoing,

Regeneron Background Technology shall exclude (i) any Information related to any Unlicensed Component and (ii) any Patent Rights that Cover the composition or use or manufacture of any Unlicensed Component (alone or in combination).

2. The following new defined terms are hereby added to Article 1 of the Agreement, effective as of the Effective Date of the Agreement:

1.275 "**[**] Research Plan**" has the meaning set forth in Section 3.2.3(f)(ii).

1.276 "**Technology Development Activities**" has the meaning set forth in Section 3.2.3(f)(iii).

1.277 "**[**] Research Plan**" has the meaning set forth in Section 3.2.3(f)(i).

3. The following new sections are hereby added to the Agreement, effective as of the Effective Date of the Agreement:

Add as new 3.2.3(f):

3.2.3 Selection of New Collaboration Targets; Technology Development Activities.

(f) Technology Development Activities.

(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**"). Under the [**] Research Plan**,** Regeneron will provide [**] antibody ligands and Alnylam will provide siRNAs for the activities under the workplan.

(ii) The Parties agree to conduct certain technology development activities related to formulation and the evaluation [**] in accordance with the mutually agreed research plan attached hereto as Schedule 1.275 (the "**[**] Research Plan**"). Under the [**] Research Plan, Alnylam will provide the siRNAs for the activities under the workplan.

(iii) The technology development activities described in clauses (i) and (ii) above may be referred to herein as the "**Technology Development Activities**." All costs associated with Technology Development Activities shall be borne by the Party performing such activities and shall not be creditable against any payments hereunder. The Parties shall conduct all Technology Development Activities in good faith. For clarity, any Materials provided by one Party to the other Party in connection with the Technology Development Activities shall be governed by Section 3.8 and, in particular, shall be used by the recipient Party solely for the intended Technology Development Activities. At least once each Calendar Quarter or upon the other Party's reasonable request, each Party will provide the other Party information in its Control generated through the Technology Development Activities.

(iv) Notwithstanding anything to the contrary (including Section 7.1.1), with respect to the Technology Development Activities, (A) any improvement, discovery or Information, patentable or otherwise, that are conceived or reduced to practice (in whole or in part) or otherwise identified, discovered, made or developed, as applicable, solely by Alnylam, its employees, agents or consultants, solely by Regeneron, its employees, agents or consultants or jointly by individuals who are employees, agents or consultants of Alnylam or its Affiliates or its or their Sublicensees, on the one hand, and individuals who are employees, agents or consultants of Regeneron or its Affiliates or its or their Sublicensees, on the other hand, under or in the course of such Technology Development Activities, and (B) any Patent Rights that Cover such improvements, discoveries or Information described in clause (A), will be classified as Joint Collaboration IP, and the Patent Rights in clause (B) will be classified as Joint Collaboration Patents.

Add as new 5.1.5:

5.1.5 during the Research Term, a non-exclusive, non-transferable (except as permitted by Section 12.2), worldwide license (or sublicense), without any right to grant sublicenses (other than to subcontractors permitted under Section 3.4.5), under any Alnylam Technology that is relevant to the Technology Development Activities assigned to Regeneron under the [**] Research Plan or the [**] Research Plan, to perform such Technology Development Activities, which license shall be fully paid-up;

Add as new 5.2.3:

5.2.3 during the Research Term, a non-exclusive, non-transferable (except as permitted by Section 12.2), worldwide license (or sublicense), without any right to grant sublicenses (other than to subcontractors permitted under Section 3.4.5), under any Regeneron Technology that is relevant to the Technology Development Activities assigned to Alnylam under the [**] Research Plan or the [**] Research Plan, to perform such Technology Development Activities, which license shall be fully paid-up;

4. 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. 1 in counterparts, each of which is deemed an original, but all of which together constitute one and the same agreement. The Amendment No. 1 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. 1 IS EXECUTED by the authorized representatives of the Parties as of the Amendment No. 1 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

Schedule 1.275
[**] Research Plan

[**]

Schedule 1.277
[**] Research Plan

[**]

EXHIBIT 31.1

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: August 3, 2023

/s/ Yvonne L. Greenstreet, MBChB, MBA

Yvonne L. Greenstreet, MBChB, MBA
Chief Executive Officer

EXHIBIT 31.2

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: August 3, 2023

/s/ Jeffrey V. Poulton

Jeffrey V. Poulton
Executive Vice President, Chief Financial Officer

EXHIBIT 32.1

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 June 30, 2023 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: August 3, 2023

/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.

EXHIBIT 32.2

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 June 30, 2023 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: August 3, 2023

/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.