

ALNYLAM PHARMACEUTICALS, INC.  
Form 10-Q  
May 02, 2019

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-Q

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

For the quarterly period ended March 31, 2019

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 77-0602661  
(State or Other Jurisdiction of (I.R.S. Employer  
Incorporation or Organization) Identification No.)

300 Third Street,

Cambridge, MA 02142  
(Address of Principal Executive Offices) (Zip Code)

(617) 551-8200

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(Registrant's Telephone Number, Including Area Code)

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

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

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

Large accelerated filer

Accelerated filer

Non-accelerated filer

Smaller reporting company

Emerging growth company

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

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

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

At April 30, 2019, the registrant had 106,536,778 shares of Common Stock, \$0.01 par value per share, outstanding.

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## ALNYLAM PHARMACEUTICALS, INC.

## CONDENSED CONSOLIDATED BALANCE SHEETS

(In thousands, except per share amounts)

(Unaudited)

	March 31, 2019	December 31, 2018
<b>ASSETS</b>		
Current assets:		
Cash and cash equivalents	\$ 724,959	\$ 420,146
Marketable debt securities	519,578	662,803
Marketable equity securities	—	1,206
Accounts receivable, net	33,801	18,760
Inventory	32,001	24,068
Prepaid expenses and other current assets	81,674	73,713
Total current assets	1,392,013	1,200,696
Property, plant and equipment, net	341,712	320,658
Operating lease right-of-use assets	226,412	—
Restricted investments	44,825	44,825
Other assets	9,037	8,623
Total assets	\$ 2,013,999	\$ 1,574,802
<b>LIABILITIES AND STOCKHOLDERS' EQUITY</b>		
Current liabilities:		
Accounts payable	\$ 22,671	\$ 59,708
Accrued expenses	106,873	112,719
Operating lease liability	16,977	—
Deferred rent	—	3,571
Deferred revenue	2,642	3,496
Total current liabilities	149,163	179,494
Operating lease liability, net of current portion	282,300	—
Deferred rent, net of current portion	—	57,920
Deferred revenue, net of current portion	478	458
Long-term debt	30,000	30,000
Other liabilities	5,072	4,965
Total liabilities	467,013	272,837
Commitments and contingencies (Note 14)		
Stockholders' equity:		
Preferred stock, \$0.01 par value per share, 5,000 shares authorized and no shares		
issued and outstanding at March 31, 2019 and December 31, 2018	—	—
Common stock, \$0.01 par value per share, 125,000 shares authorized;		
106,400 shares issued and outstanding at March 31, 2019; 101,177		
shares issued and outstanding at December 31, 2018	1,064	1,011
Additional paid-in capital	4,601,662	4,175,139

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Accumulated other comprehensive loss	(32,853 )	(33,213 )
Accumulated deficit	(3,022,887 )	(2,840,972 )
Total stockholders' equity	1,546,986	1,301,965
Total liabilities and stockholders' equity	\$ 2,013,999	\$ 1,574,802

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

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## ALNYLAM PHARMACEUTICALS, INC.

## CONDENSED CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS

(In thousands, except per share amounts)

(Unaudited)

	Three Months Ended March 31,	
	2019	2018
<b>Revenues:</b>		
Product revenues, net	\$26,291	\$—
Net revenue from collaborators	7,003	21,899
Total revenues	33,294	21,899
<b>Costs and expenses:</b>		
Cost of goods sold	3,347	—
Research and development	129,127	96,857
Selling, general and administrative	89,608	72,447
Total costs and expenses	222,082	169,304
Loss from operations	(188,788)	(147,405)
<b>Other income (expense):</b>		
Interest income	7,525	5,794
Other income	43	335
Total other income	7,568	6,129
Loss before income taxes	(181,220)	(141,276)
(Provision) benefit for income taxes	(695 )	62
Net loss	\$(181,915)	\$(141,214)
Net loss per common share - basic and diluted	\$(1.73 )	\$(1.41 )
<b>Weighted-average common shares used to compute basic and diluted net loss per</b>		
common share	105,400	99,979
<b>Comprehensive loss:</b>		
Net loss	\$(181,915)	\$(141,214)
Unrealized gain (loss) on marketable securities, net of tax	360	(420 )
Comprehensive loss	\$(181,555)	\$(141,634)

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

## ALNYLAM PHARMACEUTICALS, INC.

## CONDENSED CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY

(In thousands)

(Unaudited)

	Accumulated					
	Common Stock		Additional	Other	Comprehensive Accumulated	Total
	Shares	Amount	Paid-in Capital	Income (Loss)	Deficit	Stockholders' Equity
Balance at December 31, 2018	101,177	\$ 1,011	\$4,175,139	\$ (33,213 )	\$ (2,840,972 )	\$ 1,301,965
Exercise of common stock options, net of tax withholdings	207	3	11,406	—	—	11,409
Issuance of common stock under other types of equity plans	11	—	784	—	—	784
Issuance of common stock under equity plans, net of tax withholdings	5	—	(58 )	—	—	(58 )
Issuance of common stock, net of offering costs	5,000	50	381,850	—	—	381,900
Stock-based compensation expense related to equity-classified awards	—	—	32,541	—	—	32,541
Other comprehensive gain, net of tax	—	—	—	360	—	360
Net loss	—	—	—	—	(181,915 )	(181,915 )
Balance at March 31, 2019	106,400	\$ 1,064	\$4,601,662	\$ (32,853 )	\$ (3,022,887 )	\$ 1,546,986

	Accumulated					
	Common Stock		Additional	Other	Comprehensive Accumulated	Total
	Shares	Amount	Paid-in Capital	Income (Loss)	Deficit	Stockholders' Equity
Balance at December 31, 2017	99,667	\$ 997	\$3,947,552	\$ (34,433 )	\$ (2,147,685 )	\$ 1,766,431
Cumulative effect adjustment from the adoption of new revenue standard	—	—	—	—	68,210	68,210
Exercise of common stock options, net of tax withholdings	795	8	41,882	—	—	41,890
Issuance of common stock under other types of equity plans	4	—	567	—	—	567
	2	—	(122 )	—	—	(122 )



Issuance of common stock under  
equity plans, net of tax

withholdings

Stock-based compensation expense  
related to equity-classified

awards	—	—	19,463	—	—	19,463
Other comprehensive loss, net of tax	—	—	—	(420	)	(420 )
Net loss	—	—	—	—	(141,214	) (141,214 )
Balance at March 31, 2018	100,468	\$ 1,005	\$4,009,342	\$ (34,853	) \$(2,220,689 )	\$ 1,754,805

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

## ALNYLAM PHARMACEUTICALS, INC.

## CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS

(In thousands)

(Unaudited)

	Three Months Ended March 31,	
	2019	2018
Cash flows from operating activities:		
Net loss	\$(181,915)	\$(141,214)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation, amortization and accretion, net	12,210	3,178
Stock-based compensation	32,032	19,584
Charge for 401(k) company stock match	1,089	942
Fair value adjustments on marketable equity securities	(21 )	—
Changes in operating assets and liabilities:		
Accounts receivable, net	(15,041 )	(16,766 )
Proceeds from landlord lease incentive for tenant improvements	12,386	—
Inventory	(7,134 )	—
Prepaid expenses and other assets	(9,418 )	(27,540 )
Accounts payable	(17,133 )	(9,042 )
Accrued expenses and other	(14,731 )	(11,767 )
Deferred revenue	(834 )	26,961
Net cash used in operating activities	(188,510)	(155,664)
Cash flows from investing activities:		
Purchases of property, plant and equipment	(44,049 )	(21,257 )
Purchases of marketable debt securities	(256,996)	(358,433)
Sales and maturities of marketable securities	403,697	244,876
Net cash provided by (used in) investing activities	102,652	(134,814)
Cash flows from financing activities:		
Proceeds from exercise of stock options and other types of equity	9,083	42,094
Offering proceeds, net of costs	381,900	—
Payments for repurchase of common stock for employee tax withholding	(52 )	(572 )
Net cash provided by financing activities	390,931	41,522
Net increase (decrease) in cash, cash equivalents and restricted cash	305,073	(248,956)
Cash, cash equivalents and restricted cash, beginning of period	422,631	646,832
Cash, cash equivalents and restricted cash, end of period	\$727,704	\$397,876
Supplemental disclosure of noncash investing activities:		
Capital expenditures included in accounts payable and accrued expenses	\$13,033	\$10,437

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

We commenced operations on June 14, 2002 as a biopharmaceutical company seeking to develop and commercialize novel therapeutics based on RNA interference, or RNAi. We are committed to the advancement of our company strategy of building a multi-product, commercial biopharmaceutical company with a sustainable pipeline of RNAi therapeutics to address the needs of patients who have limited or inadequate treatment options. 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 late 2017, we filed a new drug application and a marketing authorisation application seeking regulatory approval of ONPATTRO<sup>®</sup> (patisiran), our first product, in the U.S. and Europe, respectively. In August 2018, we received approval for ONPATTRO from the United States Food and Drug Administration and began commercializing and generating product revenues in the U.S. In August 2018, we also received approval of ONPATTRO from the European Commission and in October 2018, began commercializing and generating product revenues outside of the U.S. During 2018, we also submitted regulatory applications for the approval of ONPATTRO in Japan, Canada and Switzerland, and we plan to make regulatory filings in additional markets in Europe and elsewhere throughout 2019.

We are subject to risks common to companies in our industry including, but not limited to, uncertainties relating to conducting clinical research and development, the manufacture and supply of products for clinical and commercial use, obtaining and maintaining regulatory approvals and pricing and reimbursement for our products, market acceptance, managing global growth and operating expenses, availability of additional capital, competition, obtaining and enforcing patents, stock price volatility, dependence on collaborative relationships and third-party service providers, dependence on key personnel, potential litigation, product liability claims and government investigations.

### 2. BASIS OF PRESENTATION AND PRINCIPLES OF CONSOLIDATION

The accompanying condensed consolidated financial statements of Alnylam Pharmaceuticals, Inc. 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, 2018, which were included in our Annual Report on Form 10-K that was filed with the Securities and Exchange Commission on February 14, 2019. 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, 2018. Updates to our significant accounting policies, including the updated lease accounting policy due to the adoption of the new leasing accounting standard, are discussed below and under “Recent Accounting Pronouncements.”

#### Liquidity

Based on our current operating plan, we believe that our cash, cash equivalents and marketable debt securities at March 31, 2019, together with the cash we expect to generate from product sales and under our alliances, will be sufficient to enable us to advance our Alnylam 2020 strategy for at least the next 12 months from the filing of this Quarterly Report on Form 10-Q.

## Leases

We determine whether a contract is, or contains, a lease at inception. We classify each of our leases as operating or financing considering factors such as the length of the lease term, the present value of the lease payments, the nature of the asset being leased, and the potential for ownership of the asset to transfer during the lease term. Leases with terms greater than one-year are recognized on the condensed consolidated balance sheets as right-of-use assets and lease liabilities and are measured at the present value of the fixed payments due over the expected lease term minus the present value of any incentives, rebates or abatements we expect to receive from the lessor. Options to extend a lease are included in the expected lease term if exercise of the option is deemed reasonably certain. Costs determined to be variable and not based on an index or rate are not included in the measurement of the lease liability and are expensed as incurred. The interest rate implicit in lease contracts is typically not readily determinable. As such, we utilize the appropriate incremental borrowing rate, which is the rate incurred to borrow on a collateralized basis an amount equal to the lease payments over a similar term and in a similar economic environment. We record expense to recognize fixed lease payments on a straight-line basis over the expected lease term. We have elected the practical expedient not to separate lease and non-lease components for real estate leases.

## Recent Accounting Pronouncements

In February 2016, the Financial Accounting Standards Board, or FASB, issued a new leasing standard which generally requires lessees to recognize operating and financing lease liabilities and corresponding right-of-use assets on the condensed consolidated balance sheet and to provide enhanced disclosures surrounding the amount, timing and uncertainty of cash flows arising from leasing arrangements. We adopted the new standard on January 1, 2019, using a modified retrospective basis and did not restate comparative periods. In addition, we did not elect the package of practical expedients permitted under the transition guidance that permits companies to carry forward prior conclusions related to (1) whether any expired or existing contracts are, or contain, leases, (2) the lease classification for expired or existing leases, and (3) initial direct costs for existing leases. All our leases have been classified as operating leases under the new leasing standard. We elected to combine lease and non-lease components and to keep leases with an initial term of 12 months or less off the condensed consolidated balance sheets and recognize the associated lease payments in the condensed consolidated statements of comprehensive loss on a straight-line basis over the lease term. Please read Note 8 for additional disclosures related to accounting for leases under this new standard.

The adoption of ASC 842 has a material impact on our condensed consolidated balance sheet as the standard requires us to measure and recognize a right of use asset and lease liability. As most leases do not provide an implicit rate, our incremental borrowing rate was determined based on the information available at the date of adoption to measure our lease liability. Costs determined to be variable and not based on an index or rate were not included in the measurement of the lease liability. We recognized approximately \$290 million of operating lease liabilities and approximately \$230 million of operating lease right-of-use assets on our condensed consolidated balance sheet as of January 1, 2019, which are presented as separate line items on the condensed consolidated balance sheet as of March 31, 2019. Had we not adopted the new leasing standard, we would not have had operating lease right-of-use assets or operating lease liabilities on our condensed consolidated balance sheet as of March 31, 2019. The adoption of the standard did not have a material impact on our condensed consolidated statement of comprehensive income.

In March 2017, the FASB issued a new standard that amends the amortization period for certain purchased callable debt securities held at a premium by shortening the amortization period for the premium to the earliest call date. The new standard became effective for us on January 1, 2019. This standard did not have a significant impact on our condensed consolidated financial statements and related disclosures.

In August 2018, the FASB issued amendments that eliminate, add and modify certain disclosure requirements on fair value measurements. The amendments become effective for our fiscal year, including interim periods, beginning January 1, 2020. Early adoption of the amendments in full or only the provisions that eliminate or modify the disclosure requirements for fair value measurements is permitted. We are currently evaluating the timing of our

adoption and the expected impact that these amendments could have on our disclosures.

In November 2018, the FASB issued guidance to clarify the interaction between the accounting guidance for collaborative arrangements and revenue from contracts with customers. The amendments become effective for our fiscal year, including interim periods, beginning January 1, 2020. Early adoption, including adoption in any interim period, is permitted. This guidance is required to be applied retrospectively as of the date of our adoption of the new revenue standard on January 1, 2018. We are currently evaluating the timing of our adoption and the expected impact this guidance could have on our condensed consolidated financial statements and related disclosures.

### 3. PRODUCT REVENUES, NET

During the three months ended March 31, 2019, we recorded product revenues, net of \$26.3 million, which consisted of commercial sales of ONPATTRO primarily in the U.S., along with sales in several European countries. We did not record any product revenues in the three months ended March 31, 2018.

As of March 31, 2019 and December 31, 2018, net product revenue related receivables of \$22.1 million and \$13.1 million, respectively, were included in "Accounts receivable, net."

### 4. COLLABORATION AGREEMENTS

The following table summarizes our total condensed consolidated net revenues from collaborators, for the periods indicated, in thousands:

Description	Three Months Ended March 31,	
	2019	2018
Sanofi Genzyme	\$4,117	\$18,853
The Medicines Company	1,745	1,295
Vir Biotechnology	928	1,242
Other	213	509
Total net revenues from collaborators	\$7,003	\$21,899

The following table presents the balance of our receivables and contract liabilities related to our collaboration agreements at March 31, 2019 and December 31, 2018, in thousands:

	At March 31, 2019	At December 31, 2018
Receivables included in "Accounts receivable, net"	\$11,723	\$5,625
Contract liabilities included in "Deferred revenue"	3,026	3,954

During the three months ended March 31, 2019, we recognized the following revenue as a result of the change in the contract liability balances related to our collaboration agreements, in thousands:

Revenue recognized in the period from:	Three Months Ended March 31, 2019
Amounts included in contract liability at the beginning of the period	\$ 928



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 the research and development expenses incurred by type that are directly attributable to our collaboration agreements by our collaboration partners for the periods indicated, in thousands:

	Three Months Ended March 31,					
	2019			2018		
	Sanofi			Sanofi		
	Genzyme	MDCO	Vir	Genzyme	MDCO	Vir
Research and development						
Clinical trial and manufacturing	\$4,826	\$1,612	\$294	\$10,523	\$641	\$554
External services	135	10	236	2,673	—	688
Other	59	50	129	509	—	200
Total research and						
development expenses	\$5,020	\$1,672	\$659	\$13,705	\$641	\$1,442

The research and development expenses incurred for each agreement listed in the table above consist of costs incurred for external development and manufacturing services for which we are reimbursed, licensing payments made to the counterparty to such agreement and costs directly attributable to Sanofi Genzyme transition services. In addition, these expenses include a reasonable estimate of compensation and related costs as billed to our counterparties. As part of our revenue recognition policy adopted on January 1, 2018, the costs in the above table are considered as an input in our determination of transaction price when they relate to consideration received for the delivery of goods or services. For the three months ended March 31, 2019 and 2018, we did not incur material selling, general and administrative expenses related to our collaboration agreements.

## Sanofi Genzyme Collaboration

### Collaboration Amendment

On April 8, 2019, we and Sanofi Genzyme entered into an amendment to our 2014 Sanofi Genzyme collaboration, which we refer to as the Collaboration Amendment. Under the Collaboration Amendment, we and Sanofi Genzyme agreed to conclude the research and option phase under our collaboration agreement. In connection and simultaneously with entering into the Collaboration Amendment, we and Sanofi Genzyme also entered into the Amended and Restated ALN-AT3 Global License Terms with respect to ALN-AT3 (fitusiran) and certain back-up products, which we refer to as the A&R AT3 License Terms. The A&R AT3 License Terms amend and restate the ALN-AT3 Global License Terms entered into by us and Sanofi Genzyme in January 2018 to modify certain of the business terms. The material collaboration terms for fitusiran, as previously announced, will continue unchanged.

In connection with entering into the Collaboration Amendment and the A&R AT3 License Terms, we agreed to advance, at our cost, a selected investigational asset in an undisclosed rare genetic disease through the end of IND-enabling studies. Following completion of such studies, we will transition, at our cost, such asset to Sanofi Genzyme. Thereafter, Sanofi Genzyme will fund all potential future development and commercialization costs for such asset. If this asset is developed and approved, we will be eligible to receive tiered double-digit royalties on global net sales.

No changes were made to our Exclusive License Agreement with Sanofi Genzyme, referred to as the Exclusive TTR License, pursuant to which we have global rights for the development and commercialization of ONPATTRO, together with vutrisiran and all back-up products, which remains in full force and effect.

### Amended and Restated Investor Agreement

In connection with the Collaboration Amendment, we and Sanofi Genzyme also entered into an Amended and Restated Investor Agreement, referred to as the A&R Investor Agreement, which amends and restates the Investor Agreement entered into by us and Sanofi Genzyme in February 2014, referred to as the Original Investor Agreement. Pursuant to the A&R Investor Agreement, Sanofi Genzyme is released from the lock-up restrictions under the Original Investor Agreement and is permitted to sell shares of our common stock in transactions approved by us or in fully bought block sale transactions satisfying the conditions set forth in the A&R Investor Agreement. As of January 17, 2019, Sanofi Genzyme owned 10,554,134 shares of our common stock.

Under the A&R Investor Agreement, until the earlier of (i) the fifth anniversary of the expiration of the last to expire royalty term or the earlier termination of the collaboration agreement, as amended by the Collaboration Amendment, and (ii) the date after December 31, 2021 on which the beneficial ownership of Sanofi Genzyme and its affiliates no longer represents at least 5% of the outstanding shares of common stock, Sanofi Genzyme and its affiliates will be

bound by certain “standstill” provisions, including an agreement not to propose or support a proposal to acquire us. Under the A&R Investor Agreement, Sanofi Genzyme no longer has registration rights or the conditional right to appoint one individual to our board of directors. Sanofi Genzyme continues to be entitled to certain financial information rights until Sanofi Genzyme and its affiliates no longer beneficially own at least 2.5% of our outstanding shares of common stock.

## 5. INVENTORY

The following table presents our inventory at March 31, 2019 and December 31, 2018, in thousands:

	At March 31, 2019	At December 31, 2018
Raw materials	\$9,179	\$ 8,709
Work in progress	22,687	15,262
Finished goods	135	97
Total inventory	\$32,001	\$ 24,068

## 6. FAIR VALUE MEASUREMENTS

The following tables present information about our assets that are measured at fair value on a recurring basis at March 31, 2019 and December 31, 2018, and indicate the fair value hierarchy of the valuation techniques we utilized to determine such fair value, in thousands:

Description	At March 31, 2019	Quoted Prices in Active Markets		
		(Level 1)	Significant Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
<b>Cash equivalents:</b>				
U.S. treasury securities	\$ 530,231	\$—	\$ 530,231	\$ —
Money market funds	98,236	98,236	—	—
<b>Marketable debt securities:</b>				
Certificates of deposit	3,000	—	3,000	—
Commercial paper	34,394	—	34,394	—
Corporate notes	113,253	—	113,253	—
U.S. government-sponsored enterprise securities	2,496	—	2,496	—
U.S. treasury securities	366,435	—	366,435	—
Restricted cash (money market funds)	1,478	1,478	—	—
<b>Total</b>	<b>\$ 1,149,523</b>	<b>\$ 99,714</b>	<b>\$ 1,049,809</b>	<b>\$ —</b>

Description	At December 31, 2018	Quoted Prices in Active Markets		
		(Level 1)	Significant Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
<b>Cash equivalents:</b>				
U.S. treasury securities	\$ 221,281	\$—	\$ 221,281	\$ —
Money market funds	102,445	102,445	—	—
<b>Marketable debt securities:</b>				
Certificates of deposit	8,951	—	8,951	—
Commercial paper	57,197	—	57,197	—
Corporate notes	232,410	—	232,410	—
U.S. government-sponsored enterprise securities	39,018	—	39,018	—
U.S. treasury securities	325,227	—	325,227	—
Marketable equity securities	1,206	1,206	—	—

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Restricted cash (money market funds)	1,477	1,477	—	—
Total	\$ 989,212	\$ 105,128	\$ 884,084	\$ —

During the three months ended March 31, 2019 and 2018, there were no transfers between Level 1 and Level 2 financial assets. The carrying amounts reflected in 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. The fair value of our long-term debt at March 31, 2019 and December 31, 2018, computed pursuant to a discounted cash flow technique using a market interest rate, was \$30.1 million and is considered a Level 3 fair value measurement. The effective interest rate reflects the current market rate.

## 7. MARKETABLE DEBT SECURITIES

We obtain fair value measurement data for our marketable debt securities from independent pricing services. We perform validation procedures to ensure the reasonableness of this data. This includes meeting with the independent pricing services to understand the methods and data sources used. Additionally, we perform our own review of prices received from the independent pricing services by comparing these prices to other sources and confirming those securities are trading in active markets. We did not record any impairment charges related to our marketable debt securities during the three months ended March 31, 2019 or 2018.

The following tables summarize our marketable debt securities at March 31, 2019 and December 31, 2018, in thousands:

	At March 31, 2019			
	Gross		Gross	
	Amortized	Unrealized	Unrealized	
	Cost	Gains	Losses	Fair Value
Certificates of deposit	\$3,000	\$ —	\$ —	\$3,000
Commercial paper	34,394	—	—	34,394
Corporate notes	113,281	1	(29 )	113,253
U.S. government-sponsored enterprise securities	2,496	—	—	2,496
U.S. treasury securities	896,699	25	(58 )	896,666
Total	\$1,049,870	\$ 26	\$ (87 )	\$1,049,809

	At December 31, 2018			
	Gross		Gross	
	Amortized	Unrealized	Unrealized	Fair
	Cost	Gains	Losses	Value
Certificates of deposit	\$8,951	\$ —	\$ —	\$8,951
Commercial paper	57,197	—	—	57,197
Corporate notes	232,695	—	(285 )	232,410
U.S. government-sponsored enterprise securities	39,031	—	(13 )	39,018
U.S. treasury securities	546,631	1	(124 )	546,508
Total	\$884,505	\$ 1	\$ (422 )	\$884,084

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

	At March 31, 2019	At December 31, 2018
Cash and cash equivalents	\$530,231	\$221,281
Marketable debt securities	519,578	662,803
Total	\$1,049,809	\$884,084

We classify our debt security investments based on their contractual maturity dates. The following table summarizes our available-for-sale debt securities by contractual maturity, at March 31, 2019, in thousands:

	At March 31, 2019	
	Amortized Cost	Fair Value
Less than one year	\$1,049,870	\$1,049,809
Greater than one year but less than two years	—	—
Total	\$1,049,870	\$1,049,809

## 8. LEASES

### Overview of Significant Leases

We lease three facilities for office and laboratory space in Cambridge, Massachusetts that represent substantially all of our lease obligations. An overview of these significant leases are as follows:

#### 675 West Kendall Street

In April 2015, we entered into a non-cancelable real property lease for approximately 295,000 square feet of laboratory and office space located at 675 West Kendall Street, Cambridge, Massachusetts. We intend to move our corporate headquarters and research facility to this location in 2019. The lease commenced on May 1, 2018 and monthly rent payments became due commencing on February 1, 2019 upon substantial completion of the building improvements, and continue for 15 years, with options to renew for two terms of five years each. Exercise of these options was not determined to be reasonably certain and thus was not included in the operating lease liability on the condensed consolidated balance sheet as of March 31, 2019.

#### 300 Third Street

We lease approximately 129,000 square feet of office and laboratory space located at 300 Third Street, Cambridge, Massachusetts, which to date has served as our corporate headquarters under a non-cancelable real property lease agreement dated as of September 26, 2003, as amended. The term of the lease expires on January 31, 2034, with an option to extend for two additional five-year terms. Exercise of these options was not determined to be reasonably certain and thus was not included in the operating lease liability on the condensed consolidated balance sheet as of March 31, 2019.

#### 101 Main Street

In March and May 2015, we entered into non-cancelable real property lease agreements for approximately 72,000 square feet of office space located on several floors at 101 Main Street, Cambridge, Massachusetts that will expire in March 2024 and June 2021, respectively, each with an option to renew for one five-year term. Exercise of these options was not determined to be reasonably certain and thus was not included in the operating lease liability on the condensed consolidated balance sheet as of March 31, 2019.

### Other Lease Disclosures

Our facility leases described above generally contain customary provisions allowing the landlords to terminate the leases if we fail to remedy a breach of any of our obligations under any such lease within specified time periods, or upon our bankruptcy or insolvency.

The below table summarizes our costs included in operating expenses related to leases we have entered into through March 31, 2019:

	For the Three Months Ended
Lease Cost	March 31,
Operating lease cost	\$ 9,290



Variable lease cost	5,047
Total	\$ 14,337

13

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Short-term lease costs were not material for the three months ended March 31, 2019.

Net cash paid for the amounts included in the measurement of the operating lease liability on our condensed consolidated balance sheet and included in accrued expenses and other within operating activities in our condensed consolidated statement of cash flow was \$7.1 million for the period ending March 31, 2019. The weighted-average remaining lease term and weighted-average discount rate for all leases as of March 31, 2019 was 13.9 years and 8.2%, respectively.

Future lease payments for non-cancellable operating leases as of March 31, 2019 and a reconciliation to the carrying amount of the operating lease liability presented in the condensed consolidated balance sheet as of March 31, 2019 is as follows:

Year Ending December 31,	
2019 (excluding the three months ended March 31, 2019)	\$ 11,125
2020	34,530
2021	35,776
2022	35,880
2023	35,575
2024	34,674
2025 and thereafter	356,211
Total undiscounted payments due under non-cancellable operating leases	543,771
Less imputed interest	(244,494)
Total	\$ 299,277
Current operating lease liability	\$ 16,977
Non-current operating lease liability	282,300
Total	\$ 299,277

Under the prior lease guidance, minimum payments under our non-cancelable facility leases, as of December 31, 2018, were approximately as follows, in thousands:

Year Ending December 31,	
2019	\$ 32,228
2020	34,826
2021	34,410
2022	34,826
2023	35,270
Thereafter	390,455
Total	\$ 562,015

## 9. CREDIT AGREEMENT

On April 29, 2016, we entered into a Credit Agreement, or the Credit Agreement, by and among Alnylam U.S., Inc., as the borrower, us, as a guarantor, and Wells Fargo Bank, National Association, as the lender. The Credit Agreement was entered into in connection with the planned build out of our drug substance manufacturing facility.

The Credit Agreement provides for a \$30.0 million term loan facility and matures on April 29, 2021. The proceeds of the borrowing under the Credit Agreement are to be used for working capital and general corporate purposes. Interest on borrowings under the Credit Agreement is calculated based on LIBOR plus 0.45 percent, except in the event of default. The borrower may prepay loans under the Credit Agreement at any time, without premium or penalty, subject to certain notice requirements and LIBOR breakage costs.

The obligations of the borrower and us under the Credit Agreement are secured by cash collateral in an amount equal to, at any given time, at least 100 percent of the principal amount of all term loans outstanding under such Credit Agreement at such time. At each of March 31, 2019 and December 31, 2018, we recorded \$30.0 million of cash collateral in connection with the Credit Agreement as restricted investments on our condensed consolidated balance sheets. The Credit Agreement contains limited representations and warranties and limited affirmative and negative covenants, including quarterly reporting obligations, as well as certain customary events of default.

## 10. EQUITY

In January 2019, we sold an aggregate of 5,000,000 shares of our common stock through an underwritten public offering at a price to the public of \$77.50 per share. As a result of the offering, we received aggregate net proceeds of \$381.9 million after deducting underwriting discounts and commissions and other offering expenses of approximately \$5.6 million.

## 11. STOCK-BASED COMPENSATION

Stock-based compensation expenses included in operating costs and expenses are as follows, in thousands:

	Three Months Ended March 31,	
	2019	2018
Research and development	\$16,125	\$10,137
Selling, general and administrative	15,907	9,447
Total stock-based compensation	\$32,032	\$19,584

## 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. Potential common shares consist of shares issuable upon 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). 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 for the periods presented the potential common shares (prior to consideration of the treasury stock method) excluded from the calculation of net loss per common share because their inclusion would be anti-dilutive, in thousands:

	At March 31,	
	2019	2018
Options to purchase common stock	13,868	12,515
Unvested restricted common stock	717	157

14,585 12,672

## 13. RECONCILIATION OF CASH, CASH EQUIVALENTS AND RESTRICTED CASH

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

	At March 31,	
	2019	2018
Cash and cash equivalents	\$724,959	\$396,149
Restricted cash included in prepaid expenses and other current assets	439	—
Restricted cash included in long-term other assets	2,306	1,727
Total cash, cash equivalents, and restricted cash shown in the		
condensed consolidated statements of cash flows	\$727,704	\$397,876

## 14. COMMITMENTS AND CONTINGENCIES

## Manufacturing Facility

In April 2016, we purchased 12 acres of undeveloped land in Norton, Massachusetts. We are constructing a manufacturing facility at this site for drug substance for clinical and commercial use. At March 31, 2019 and December 31, 2018, property, plant and

equipment, net, on our condensed consolidated balance sheets reflect \$240.7 million and \$227.7 million, respectively, of land and associated costs related to the construction of our drug substance manufacturing facility.

### Litigation

From time to time, we are a party to 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. 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.

### Securities Litigation

On September 26, 2018, Caryl Hull Leavitt, individually and on behalf of all others similarly situated, filed a class action complaint for violation of federal securities laws against us, our Chief Executive Officer and our Chief Financial Officer in the United States District Court for the Southern District of New York. The complaint purports to bring a federal securities class action on behalf of a class of persons who acquired our securities between February 15, 2018 and September 12, 2018 and seeks to recover damages caused by defendants' alleged violations of the federal securities laws and to pursue remedies under Sections 10(b) and 20(a) of the Securities Exchange Act of 1934, as amended, and Rule 10b-5 promulgated thereunder. The complaint alleges, among other things, that the defendants made materially false and misleading statements related to the efficacy and safety of our product, ONPATTRO. The plaintiff seeks, among other things, the designation of this action as a class action, an award of unspecified compensatory damages, interest, costs and expenses, including counsel fees and expert fees, and other relief as the court deems appropriate.

By stipulation of the parties and Order of the Court dated November 20, 2018, the action was transferred to the United States District Court for the District of Massachusetts. Motions for the appointment of lead plaintiff and lead counsel were required to be filed by November 26, 2018. There are three such motions currently pending. We anticipate that an amended complaint will be filed following the Court's appointment of lead plaintiff and lead counsel.

We believe that the allegations contained in the complaint are without merit and intend to defend the case vigorously. We cannot predict at this point the length of time that this action will be ongoing or the liability, if any, which may arise therefrom.

### Dicerna Litigation

On June 10, 2015, we filed a trade secret misappropriation lawsuit against Dicerna Pharmaceuticals, Inc., or Dicerna, in the Superior Court of Middlesex County, Massachusetts seeking to stop misappropriation by Dicerna of our confidential, proprietary and trade secret information related to the RNAi assets we purchased from Merck Sharp & Dohme Corp., including certain N-acetylgalactosamine, or GalNAc, conjugate technology. In addition to permanent injunctive relief, we were also seeking monetary damages from Dicerna.

On April 18, 2018, we and Dicerna entered into a settlement agreement resolving all ongoing litigation between the companies. Under the terms of the settlement agreement, Dicerna was required to pay us an aggregate of \$25.0 million, including an upfront cash payment of \$2.0 million and 983,208 shares of Dicerna common stock,

valued at \$10.0 million, that were received in the second quarter of 2018, and an additional \$13.0 million over the next four years, the timing of which was dependent upon revenue Dicerna received pursuant to future partnerships and collaborations related to GalNAc-conjugated RNAi research and development. As a result of Dicerna collaborations entered into subsequent to the settlement agreement, we were due the remaining \$13.0 million as of December 31, 2018, of which \$2.5 million was received in December 2018 and \$10.5 million was received in January 2019.

## 15. SUBSEQUENT EVENTS

On April 8, 2019, we entered into a global, strategic collaboration with Regeneron Pharmaceuticals, Inc., or Regeneron, to discover, develop and commercialize RNAi therapeutics for a broad range of diseases by addressing disease targets expressed in the eye and central nervous system, or CNS, in addition to a select number of targets expressed in the liver. In connection with the collaboration, Regeneron has agreed to make a \$400.0 million upfront payment to us and we are eligible to receive up to an additional \$200.0 million in milestone payments upon achievement of certain criteria during early clinical development for the eye and CNS programs. The companies plan to advance programs directed to 30 targets during the initial five-year discovery period, which may be

extended under certain circumstances for an additional two years. Regeneron has the option to extend the initial research term upon payment of a research term extension fee. 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 collaboration reaches steady state.

In conjunction with the collaboration agreement, Regeneron entered into a stock purchase agreement with us whereby Regeneron has agreed to purchase \$400.0 million of our common stock at a price per share of \$90.00 (4.44 million shares), based on the volume-weighted average price over the fifteen-trading-day period preceding execution of the stock purchase agreement.

The collaboration will become effective upon closing of the equity transaction, subject to clearance under the Hart-Scott Rodino Antitrust Improvements Act of 1976, as amended, and other customary closing conditions, which we expect to occur in the second quarter of 2019.



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

This Quarterly Report on Form 10-Q contains forward-looking statements that involve risks and uncertainties. The statements contained in this Quarterly Report on Form 10-Q that are not purely historical are forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. Without limiting the foregoing, the words “may,” “will,” “should,” “could,” “expects,” “plans,” “intends,” “anticipates,” “believes,” “estimates,” “predicts,” “potential,” “continues” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these words. All forward-looking statements included in this Quarterly Report on Form 10-Q are based on information available to us up to, and including, the date of this document, and we expressly disclaim any obligation to update any such forward-looking statements to reflect events or circumstances that arise after the date hereof. Our actual results could differ materially from those anticipated in these forward-looking statements as a result of certain important factors, including those set forth in this Item 2 — “Management’s Discussion and Analysis of Financial Condition and Results of Operations,” as well as under Part II, Item 1A — “Risk Factors” and elsewhere in this Quarterly Report on Form 10-Q. You should carefully review those factors and also carefully review the risks outlined in other documents that we file from time to time with the Securities and Exchange Commission, or SEC.

### Overview

We are a global commercial-stage biopharmaceutical company developing novel therapeutics based on RNA 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 disease-causing proteins, thus preventing them from being made. We believe this is a revolutionary approach with the potential to transform the care of patients with genetic and other diseases. Our efforts to advance this revolutionary approach culminated with the approval in 2018 of the first ever RNAi therapeutic, ONPATTRO® (patisiran), for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis, or hATTR amyloidosis, in adults in the U.S. and for the treatment of hATTR amyloidosis in adult patients with Stage 1 or Stage 2 polyneuropathy in the European Union, or EU.

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 lipid nanoparticle (LNP) or N-acetylgalactosamine (GalNAc) conjugate approach to enable hepatic delivery of siRNAs. For delivery to the central nervous system, or CNS, and the eye (ocular delivery), we intend to utilize an alternative conjugate approach. Our focus is on clinical indications where there is a high unmet need, 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.

We are committed to the advancement of our Alnylam 2020 strategy of building a multi-product, commercial biopharmaceutical company with a sustainable pipeline of RNAi therapeutics to address the needs of patients who have limited or inadequate treatment options. Specifically, our broad pipeline of investigational RNAi therapeutics is focused in four Strategic Therapeutic Areas, or “STArS:” Genetic Medicines; Cardio-Metabolic Diseases; Hepatic Infectious Diseases; and CNS/Ocular Diseases. In August 2018, we received regulatory approval for ONPATTRO from the United States Food and Drug Administration, or FDA, for the treatment of the polyneuropathy of hATTR amyloidosis in adults. Also, in August 2018, the European Commission, or EC, granted marketing authorisation for ONPATTRO for the treatment of hATTR amyloidosis in adults with Stage 1 or Stage 2 polyneuropathy. We began selling ONPATTRO in the U.S. in August 2018 and in Germany in October 2018, and are now marketing ONPATTRO in several additional countries in Europe. During 2018, we also submitted regulatory applications for the approval of ONPATTRO in Japan, Canada and Switzerland. Regulatory filings in additional markets in Europe and elsewhere are planned throughout 2019.

In addition to our first marketed product, we have five late-stage investigational programs advancing toward potential commercialization. Our most advanced investigational RNAi therapeutic, givosiran, targets aminolevulinic acid synthase 1, or ALAS1, for the treatment of patients with acute hepatic porphyria, or AHP. In mid-April 2019, we reported positive complete results from our ENVISION Phase 3 study of givosiran. Based on the positive ENVISION data, we plan to submit a new drug application, or NDA, and a marketing authorisation application, or MAA, for givosiran in mid-2019. Our other four late-stage investigational programs include our other wholly owned programs: lumasiran for the treatment of primary hyperoxaluria type 1, or PH1, and vutrisiran for the treatment of ATTR amyloidosis. Inclisiran for the treatment of hypercholesterolemia and atherosclerotic cardiovascular disease is being advanced by our partner, The Medicines Company, or MDCO, and fitusiran for the treatment of hemophilia is being advanced by our partner Sanofi Genzyme, the specialty care global business unit of Sanofi.

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 Sanofi Genzyme, MDCO, Vir Biotechnology, Inc., or Vir, and Regeneron Pharmaceuticals, Inc., or Regeneron.

In April 2019, we entered into a global, strategic collaboration with Regeneron to discover, develop and commercialize RNAi therapeutics for a broad range of diseases by addressing therapeutic targets expressed in the eye and CNS, in addition to a select number of targets expressed in the liver. A description of our Regeneron collaboration and the related stock purchase agreement is described in more detail below under the heading “Strategic Alliances.”

In January 2019, we sold 5,000,000 shares of our common stock through an underwritten public offering at a price to the public of \$77.50 per share. As a result of the offering, we received aggregate net proceeds of approximately \$381.9 million.

We have incurred significant losses since we commenced operations in 2002 and expect such losses to continue for the foreseeable future. At March 31, 2019, we had an accumulated deficit of \$3.02 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 operations, continued management and growth of our patent portfolio, collaborations and general corporate activities, we expect to incur additional operating losses for the foreseeable future. We also anticipate that our operating results will 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 noted above, in August 2018, received regulatory approval from the FDA and EC for our first product, ONPATTRO. As a result of the regulatory approval of ONPATTRO, we began to generate net revenues from product sales during the third quarter of 2018. 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 ONPATTRO or any other approved products in the future. A substantial portion of our total revenues in recent years has been derived from collaboration revenues from strategic alliances with Sanofi Genzyme and MDCO. In addition to revenues from the commercial sale of ONPATTRO 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, which may include license and other fees, funded research and development, milestone payments and royalties on product sales by our licensors, and proceeds from the sale of equity or debt.

#### Research and Development

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

Our broad pipeline including one approved product and multiple 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 product development programs as of April 30, 2019. It identifies those programs in which we have achieved human proof-of-concept, or POC, by demonstrating target gene knockdown and/or additional evidence of activity in clinical studies, those programs for which we have received Breakthrough Therapy Designation from the FDA, the stage of our programs and our commercial rights to such programs:

During the first quarter of 2019 and recent period, we reported the following updates from ONPATTRO commercialization and our late-stage clinical programs:

#### Commercial

• We achieved global ONPATTRO net product revenues for the first quarter of 2019 of \$26.3 million.

#### Late-Stage Clinical Development

• We continued to advance patisiran (the non-branded name for ONPATTRO) for the treatment of ATTR amyloidosis, and aligned with the FDA on the design of APOLLO-B, a randomized, double-blind, placebo-controlled Phase 3 study of patisiran in hereditary and wild-type ATTR amyloidosis patients with cardiomyopathy, with the goal of starting the trial in mid-2019.

• We continued to advance vutrisiran, a subcutaneously administered investigational RNAi therapeutic in development for the treatment of ATTR amyloidosis:

- o Continued enrollment in the HELIOS-A Phase 3 study of vutrisiran in hereditary ATTR amyloidosis patients; and
- o Plan to initiate additional Phase 3 studies, including in hereditary and wild-type ATTR amyloidosis cardiomyopathy, in late 2019.

• We continued to advance givosiran, a subcutaneously administered investigational RNAi therapeutic in development for the treatment of AHP, reporting positive complete results from our ENVISION Phase 3 study in April 2019. We are on track to complete submission of an NDA and submit an MAA for givosiran in mid-2019.

• We continued to advance lumasiran, a subcutaneously administered investigational RNAi therapeutic in development for the treatment of PH1, continuing enrollment in the ILLUMINATE-A Phase 3 study of lumasiran in PH1 patients aged six or older with mild-to-moderate renal impairment. We remain on track to report results by year-end 2019. We also initiated ILLUMINATE-B, a global Phase 3 pediatric study of lumasiran in PH1 patients under six years of age.

• Our partner, MDCO, announced in April 2019 that the Independent Data Monitoring Committee for ongoing inclisiran Phase 3 clinical trials (ORION 9, 10, and 11) conducted its sixth planned review of safety and efficacy data from the ORION trials and recommended that the trials continue without modification.

• Enrollment in the ATLAS Phase 3 program for fitusiran, a subcutaneously administered investigational RNAi therapeutic in development for the treatment of hemophilia A or B with and without inhibitors, is ongoing and is being led by our partner, Sanofi Genzyme.

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. Moreover, there are uncertainties specific to any new field of drug discovery, including RNAi. The success of ONPATTRO 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 the period, if any, in which material net cash inflows will commence from any approved product. Any failure to complete any stage of the development of any potential products in a timely manner or successfully launch, market and sell any approved product, including ONPATTRO, 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 projects on schedule, 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 Genetic Medicine pipeline, we formed a broad strategic alliance with Sanofi Genzyme in 2014. In January 2018, we and Sanofi Genzyme amended our 2014 Sanofi Genzyme 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, vutrisiran and any back-up products, and the ALN-AT3 Global License Terms, referred to as the AT3 License Terms, under which Sanofi Genzyme 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 Genzyme agreed to further amend the 2014 Sanofi Genzyme collaboration to conclude the research and option phase and to amend and restate the AT3 License Terms, referred to as the A&R AT3 License Terms, to modify certain of the business terms. The material collaboration terms for fitusiran will continue unchanged. In connection with entering into the 2019 amendment and the A&R AT3 License Terms, we agreed to advance, at our cost, a selected investigational asset in an undisclosed rare genetic disease through the end of IND-enabling studies. Following completion of such studies, we will transition, at our cost, such asset to Sanofi Genzyme. Thereafter, Sanofi Genzyme will fund all potential future development and commercialization costs for such asset. If this asset is approved, we will be eligible to receive tiered double-digit royalties on global net sales.

With respect to our Cardio-Metabolic Disease pipeline, we intend to seek future strategic alliances for these programs, under which we may retain certain product development and commercialization rights, or we may structure as global alliances, as we did in our collaboration with MDCO 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.

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 hepatitis B virus, or HBV, infection.

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 connection with the collaboration, Regeneron has agreed to make a \$400.0 million upfront payment to us and we are eligible to receive up to an additional \$200.0 million in milestone payments upon achievement of certain criteria during early clinical development for the eye and CNS programs.

The companies plan to advance programs directed to 30 targets during the initial five-year discovery period, which may be extended under certain circumstances for an additional two years. Regeneron has the option to extend the initial research term upon payment of a research term extension fee. 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 collaboration reaches steady state.

In conjunction with the collaboration agreement, Regeneron entered into a stock purchase agreement with us whereby Regeneron has agreed to purchase \$400.0 million of our common stock at a price per share of \$90.00 (4.44 million shares), based on the volume-weighted average price over the fifteen-trading-day period preceding execution of the stock purchase agreement.

The collaboration will become effective upon closing of the equity transaction, subject to clearance under the Hart-Scott Rodino Antitrust Improvements Act of 1976, as amended, and other customary closing conditions, which we expect to occur in the second quarter of 2019.

### Intellectual Property

The strength of our intellectual property portfolio relating to the development and commercialization of siRNAs as therapeutics is essential to our business strategy. We own or license issued patents and pending patent applications in the U.S. and in key markets around the world claiming fundamental features of siRNAs and RNAi therapeutics as well as those claiming crucial chemical modifications and promising delivery technologies. 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.

We believe that no other company possesses a portfolio of such broad and exclusive rights to the patents and patent applications required for the commercialization of RNAi therapeutics. In addition, we are very active in our evaluation of third-party technologies. Given the importance of our intellectual property portfolio to our business operations, we intend to vigorously enforce our rights and defend against challenges that have arisen or may arise in this area.

### 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, 2018, which we filed with the SEC on February 14, 2019. 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 for the periods indicated, in thousands:

Description	Three	Three	Dollar	% of
	Months	Months		
	Ended	Ended	Change	Change
	March 31,	March 31,		
	2019	2018		

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Revenues	\$33,294	\$21,899	\$11,395	52	%
Operating costs and expenses	222,082	169,304	52,778	31	%
Loss from operations	(188,788 )	(147,405 )	(41,383 )	28	%
Net loss	\$(181,915 )	\$(141,214 )	\$(40,701 )	29	%



## Discussion of Results of Operations

## Revenues

The following table summarizes our total condensed consolidated revenues, in thousands:

Description	Three Months Ended March 31, 2019	Three Months Ended March 31, 2018	Dollar Change	% of Change
Product revenues, net	\$ 26,291	\$ —	\$26,291	N/A
Net revenue from collaborators	7,003	21,899	(14,896)	(68 %)
Total revenues	\$ 33,294	\$ 21,899	\$ 11,395	52 %

## Product revenues, net

We began to record net product revenues following regulatory approval of ONPATTRO in the U.S. and EU in August 2018 and its subsequent commercial launch in the U.S. and in several countries in Europe during the third and fourth quarters of 2018, respectively. During the three months ended March 31, 2019, we recognized \$26.3 million of net product revenues related to sales of ONPATTRO. We expect net product revenues to increase for the remainder of 2019 as compared to 2018 primarily due to a full year of ONPATTRO sales in 2019 and launches in additional geographies, as we continue to execute on our global launch of ONPATTRO.

## Net revenues from collaborators

The following table summarizes our total condensed consolidated net revenues from collaborators under our research and development collaborations, in thousands:

Description	Three Months Ended March 31, 2019	Three Months Ended March 31, 2018	Dollar Change	% of Change
Sanofi Genzyme	\$ 4,117	\$ 18,853	\$(14,736)	(78 %)
MDCO	1,745	1,295	450	35 %
Vir	928	1,242	(314 )	(25 %)
Other	213	509	(296 )	(58 %)
Total net revenues from collaborators	\$ 7,003	\$ 21,899	\$(14,896)	(68 %)

Net revenues from collaborators decreased during the three months ended March 31, 2019 as compared to the three months ended March 31, 2018 due primarily to a decrease in reimbursable activities in connection with our collaboration agreement with Sanofi Genzyme.

We expect net revenues from collaborators to increase during the remainder of 2019 following closing of the Regeneron collaboration agreement.

## Operating costs and expenses

The following tables summarize our operating costs and expenses, in thousands:

Description	Three Months Ended March 31, 2019	Three Months Ended March 31, 2018	Dollar Change	% of Change	
Cost of goods sold	\$ 3,347	\$ —	\$3,347	N/A	
Research and development	129,127	96,857	32,270	33	%
Selling, general and administrative	89,608	72,447	17,161	24	%
Total operating costs and expenses	\$ 222,082	\$ 169,304	\$ 52,778	31	%

Cost of Goods Sold. Cost of goods sold includes the cost of producing and distributing inventories that are related to ONPATTRO product revenues and third-party royalties. We began capitalizing ONPATTRO inventory during the third quarter of 2018 in connection with FDA approval and based upon our expectation that these costs are recoverable through commercialization of

ONPATTRO. Prior to the capitalization of ONPATTRO inventory (zero-cost inventory), costs were recorded as research and development expenses in our condensed consolidated statements of comprehensive loss. The cost of goods sold during the three months ended March 31, 2019 only reflects a portion of the manufacturing cost of ONPATTRO and third-party royalties. At March 31, 2019, we expect to continue selling zero-cost inventory over the next 12 to 15 months. We estimate cost of goods sold as a percentage of ONPATTRO product revenues, net will be in the mid- to high teens subsequent to the utilization of our zero-cost inventory.

We expect that cost of goods sold will increase during the remainder of 2019 as compared to 2018 primarily as a result of an expected increase in ONPATTRO sales.

Research and development. The following table summarizes the components of our research and development expenses for the periods indicated, in thousands:

Description	Three Months Ended March 31, 2019	Three Months Ended March 31, 2018	Dollar Change	% of Change	
Research and development					
Compensation and related	\$ 36,377	\$ 30,266	\$ 6,111	20	%
Clinical trial	21,235	20,135	1,100	5	%
Stock-based compensation	16,125	10,137	5,988	59	%
External services	13,530	13,090	440	3	%
Manufacturing	13,366	10,758	2,608	24	%
Facilities-related	12,227	7,553	4,674	62	%
License Fees	7,600	—	7,600	N/A	
Lab supplies and materials	3,093	2,128	965	45	%
Other	5,574	2,790	2,784	100	%
Total research and development expenses	\$ 129,127	\$ 96,857	\$ 32,270	33	%

Research and development expenses increased during the three months ended March 31, 2019 as compared to the three months ended March 31, 2018 due primarily to increased license fees related to regulatory milestones deemed probable as a result of positive complete results for our givosiran Phase 3 study, and increased compensation and related expenses, including stock-based compensation, and facilities-related expenses, in each case as a result of growth in headcount to support our goals for 2020. In addition, research and development expenses increased due to an increase in stock-based compensation expense related to the accounting for performance-based stock awards as a result of the commercial launch of ONPATTRO and clinical achievements with respect to our givosiran Phase 3 study.

During the three months ended March 31, 2019 and 2018, in connection with advancing activities under our collaboration agreements, we incurred research and development expenses, primarily related to external development and manufacturing services. The following table summarizes the expenses incurred under our collaboration agreements by collaboration partner for the periods indicated, in thousands:

	Three Months Ended March 31,	
	2019	2018
Sanofi Genzyme	\$5,020	\$13,705
MDCO	1,672	641
Vir	659	1,442
Total	\$7,351	\$15,788

We expect to continue to devote a substantial portion of our resources to research and development expenses to support our goals for 2020. We expect that research and development expenses will increase during the remainder of 2019 as compared to 2018 as we continue to develop our pipeline and advance our product candidates into later-stage development, hire additional employees and prepare regulatory submissions. 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.

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Selling, general and administrative. The following table summarizes the components of our selling, general and administrative expenses for the periods indicated, in thousands:

Description	Three Months Ended March 31, 2019	Three Months Ended March 31, 2018	Dollar Change	% of Change	
Selling, general and administrative					
Compensation and related	\$ 30,123	\$ 23,611	\$6,512	28	%
Consulting and professional services	25,826	30,430	(4,604 )	(15	%)
Stock-based compensation	15,907	9,447	6,460	68	%
Facilities-related	8,158	3,555	4,603	129	%
Other	9,594	5,404	4,190	78	%
Total general and administrative expenses	\$ 89,608	\$ 72,447	\$ 17,161	24	%

Selling, general and administrative expenses increased during the three months ended March 31, 2019 as compared to the three months ended March 31, 2018 due primarily to an increase in commercial and medical affairs headcount and commercial-related services to support corporate growth and the continued global launch of ONPATTRO. In addition, selling, general and administrative expenses increased due to an increase in stock-based compensation expense related to growth in headcount and the accounting for performance-based stock awards as a result of the commercial launch of ONPATTRO and clinical achievements with respect to our givosiran Phase 3 study.

We expect that selling, general and administrative expenses will increase during the remainder of 2019 as compared to 2018 as we continue to grow our operations, including the continued build-out of our global commercial infrastructure to support ONPATTRO and potentially additional product launches, but expect that stock-based compensation expenses will be variable due to our determination regarding the probability of vesting for performance-based awards.

#### Liquidity and Capital Resources

The following table summarizes our cash flow activities for the periods indicated, in thousands:

	Three Months Ended March 31,	
	2019	2018
Net loss	\$(181,915)	\$(141,214)
Adjustments to reconcile net loss to net cash used in		
operating activities	45,310	23,704
Changes in operating assets and liabilities	(51,905 )	(38,154 )
Net cash used in operating activities	(188,510)	(155,664)
Net cash provided by (used in) investing activities	102,652	(134,814)
Net cash provided by financing activities	390,931	41,522
Net increase (decrease) in cash, cash equivalents and		
restricted cash	305,073	(248,956)

Cash, cash equivalents and restricted cash, beginning of

period	422,631	646,832
Cash, cash equivalents and restricted cash, end of		
period	\$727,704	\$397,876

Since we commenced operations in 2002, we have generated significant losses. At March 31, 2019, we had an accumulated deficit of \$3.02 billion. At March 31, 2019, we had cash, cash equivalents and marketable debt securities of \$1.24 billion, compared to \$1.08 billion at December 31, 2018.

In January 2019, we sold an aggregate of 5,000,000 shares of our common stock through an underwritten public offering at a price to the public of \$77.50 per share. As a result of the offering, we received aggregate net proceeds of \$381.9 million, after deducting underwriting discounts and commissions and other estimated offering expenses of \$5.6 million.

We invest primarily in money market funds, U.S. government-sponsored enterprise securities, U.S. treasury securities, high-grade corporate notes, certificates of deposit and commercial paper. Corporate notes may also include foreign bonds denominated in U.S. dollars. Our investment objectives are, primarily, to assure liquidity and preservation of capital and, secondarily, to obtain investment income. All of our investments in marketable debt securities are recorded at fair value and are available-for-sale. Fair value is determined based on quoted market prices and models using observable data inputs. We have not recorded any impairment charges to our marketable debt securities during the three months ended March 31, 2019 and 2018.

#### Operating activities

We have required significant amounts of cash to fund our operating activities as a result of net losses since our inception. Cash used in operating activities increased during the three months ended March 31, 2019 compared to the same period in 2018 primarily due to the increase in our net loss attributable to increased operating expenses to support overall growth, offset by an increase in revenues due to approval of ONPATTRO in the third quarter of 2018.

We expect that we will require significant amounts of cash to fund our operating activities for the foreseeable future as we continue to execute on our Alnylam 2020 strategy through the advancement of our research, development, pre-commercial and commercial initiatives. The actual amount of overall expenditures will depend on numerous factors, including the timing of net product revenues and expenses, the timing and terms of collaboration agreements or other strategic transactions, if any, and the timing and progress of our research, development and commercialization efforts.

#### Investing activities

For the three months ended March 31, 2019 and 2018, net cash provided by investing activities included activities related to our marketable debt securities in accordance with management of our liquidity needs. For the three months ended March 31, 2019 and 2018, net cash used in investing activities included purchases of property, plant and equipment of \$44.0 million and \$21.3 million, respectively, primarily in connection with construction of our drug substance manufacturing facility.

#### Financing activities

For the three months ended March 31, 2019, net cash of \$390.9 million provided by financing activities was due primarily to proceeds of \$381.9 million received from our January 2019 underwritten public offering and proceeds received from the issuance of common stock in connection with stock option exercises. For the three months ended March 31, 2018, net cash of \$41.5 million provided by financing activities was due primarily to proceeds received from the issuance of common stock in connection with stock option exercises.

#### Operating Capital Requirements

We currently have programs focused on a number of therapeutic areas and, in August 2018, received our first product approvals in the U.S. and EU for ONPATTRO. As a result, we began to generate net revenues from product sales during the third quarter of 2018. However, our ongoing development efforts may not be successful and we may not be able to commence sales of any other products in the future. In addition, we anticipate that we will continue to generate significant losses for the foreseeable future 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 operations, continued management and growth of our intellectual property including our patent portfolio, collaborations and general corporate activities. In addition, we are expanding our manufacturing capabilities, including through construction of a drug substance manufacturing facility in Norton, Massachusetts.

Based on our current operating plan, we believe that our cash, cash equivalents and marketable debt securities at March 31, 2019, together with the cash we expect to generate from product sales and under our current alliances, including, upon closing, our recent collaboration with Regeneron, will be sufficient to enable us to advance our Alnylam 2020 strategy for multiple years from the filing of this quarterly report on Form 10-Q. For reasons discussed below, we may require significant additional funds earlier than we currently expect in order to continue to commercialize ONPATTRO and to develop, conduct clinical trials for, manufacture and, if approved, commercialize additional product candidates.



In the future, we may seek additional funding through new collaborative arrangements and public or private financings. Additional funding may not be available to us on acceptable terms or at all. Moreover, the terms of any additional financing may further adversely affect the holdings or the rights of our stockholders. For example, 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 funds to us, future investors may demand, and may be granted, rights superior to those of existing stockholders. If we are unable to obtain funding on a timely basis, we may be required to significantly delay or curtail one or more of our research or development programs and our ability to achieve our goals for 2020 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. Even if we are able to raise additional funds in a timely manner, our future capital requirements may vary from what we expect and will depend on many factors, including:

- our continued progress in demonstrating that siRNAs can be active as drugs and achieve desired clinical effects;
  - progress in our research and development programs, 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;
    - our ability to maintain and establish additional collaborative arrangements and/or new business initiatives;
    - the resources, time and costs required to successfully initiate and complete our pre-clinical and clinical trials, 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 resources, time and cost required for the preparation, filing, prosecution, maintenance and enforcement of patent claims;
  - the costs associated with legal activities, including litigation, arising in the course of our business activities and our ability to prevail in any such legal disputes; and
  - the timing, receipt and amount of sales and royalties, if any, from ONPATPRO and our other potential products.
- Contractual Obligations and Commitments

The disclosure of our contractual obligations and commitments is set forth under the heading “Management’s Discussion and Analysis of Financial Condition and Results of Operations—Contractual Obligations” in our Annual Report on Form 10-K for the year ended December 31, 2018. There have been no material changes in our contractual obligations and commitments since December 31, 2018.

#### Recent Accounting Pronouncements

Please read Note 2 to our condensed consolidated financial statements included in Item 1, “Financial Statements (Unaudited),” of this Quarterly Report on Form 10-Q for a description of recent accounting pronouncements applicable to our business.

### ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK.

As part of our investment portfolio, we own financial instruments that are sensitive to market risks. The investment portfolio is used to preserve our capital until it is required to fund operations, including our research, development and commercial activities. Our marketable debt securities consist of primarily U.S. government-sponsored enterprise securities, U.S. treasury securities, high-grade corporate notes, and commercial paper. Corporate notes may also include foreign bonds denominated in U.S. dollars. All of our investments in debt securities are classified as available-for-sale and are recorded at fair value. Our available-for-sale investments in debt securities are sensitive to changes in interest rates and changes in the credit ratings of the issuers. Interest rate changes would result in a change in the net fair value of these financial instruments due to the difference between the market interest rate and the market interest rate at the date of purchase of the financial instrument. If market interest rates were to increase immediately and uniformly by 50 basis points, or one-half of a percentage point, from levels at March 31, 2019, the net fair value of our interest-sensitive financial instruments would have resulted in a hypothetical decline of \$0.9 million. We currently do not seek to hedge this exposure to fluctuations in interest rates. A downgrade in the credit rating of an issuer of a debt security or further deterioration of the credit markets could result in a decline in the fair value of the debt instruments. Our investment guidelines prohibit investment in auction rate securities and we do not believe we have any direct exposure to losses relating from mortgage-based securities or derivatives related thereto such as credit-default swaps. As we build our foreign operations, we face exposure to movements in foreign currency exchange rates, primarily the Euro, Swiss Franc and British Pound against the U.S. dollar. We will continue to evaluate strategies to mitigate foreign exchange risk, including the implementation of a foreign currency hedging program. Historically, foreign currency fluctuations have not been material. We did not record any impairment charges to our marketable debt securities during the three months ended March 31, 2019.

### ITEM 4. CONTROLS AND PROCEDURES.

Our management, with the participation of our Chief Executive Officer (principal executive officer) and senior vice president, Chief Financial Officer (principal financial officer), evaluated the effectiveness of our disclosure controls and procedures as of March 31, 2019. The term “disclosure controls and procedures,” as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC’s rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company’s management, including its principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of March 31, 2019, our Chief Executive Officer and senior vice president, Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

During the three months ended March 31, 2019, we implemented certain internal controls as a result of our adoption of the new lease standard on January 1, 2019. There were no other changes in our internal control over financial reporting (as defined in Rules 13a–15(f) and 15d–15(f) under the Exchange Act) occurred during the three months ended March 31, 2019 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 14, Commitments and Contingencies – Litigation, 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

Our business is subject to numerous risks. We caution you that the following important factors, among others, could cause our actual results to differ materially from those expressed in forward-looking statements made by us or on our behalf in filings with the SEC, press releases, communications with investors and oral statements. All statements other than statements relating to historical matters should be considered forward-looking statements. When used in this report, the words “believe,” “expect,” “plan,” “anticipate,” “estimate,” “predict,” “may,” “could,” “should,” “intend,” “will,” “tend,” and “may” or similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these words. Any or all of our forward-looking statements in this quarterly report on Form 10-Q and in any other public statements we make may turn out to be wrong. They can be affected by inaccurate assumptions we might make or by known or unknown risks and uncertainties. Many factors mentioned in the discussion below will be important in determining future results. Consequently, no forward-looking statement can be guaranteed. Actual future results may vary materially from those anticipated in forward-looking statements. We explicitly disclaim any obligation to update any forward-looking statements to reflect events or circumstances that arise after the date hereof. You are advised, however, to consult any further disclosure we make in our reports filed with the SEC.

#### Risks Related to Our Business

#### Risks Related to Being a Commercial Company

We have limited experience as a commercial company and the marketing and sale of ONPATTRO or any future products may be unsuccessful or less successful than anticipated.

In August 2018, the FDA approved ONPATTRO (patisiran) lipid complex injection for the treatment of the polyneuropathy of hATTR amyloidosis in adults in the U.S., and the EC granted marketing authorisation for ONPATTRO for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy in the EU. While we have launched ONPATTRO in the U.S. and in several countries in Europe, we have limited experience as a commercial company and there is limited information about our ability to successfully overcome many of the risks and uncertainties encountered by companies commercializing products in the biopharmaceutical industry. We also have several product candidates in late-stage clinical development. To execute our business plan, in addition to successfully marketing and selling ONPATTRO, we will need to successfully:

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execute product development activities using new technologies related to both RNAi and to the delivery of siRNAs to the relevant tissues and cells;

• build and maintain a strong intellectual property portfolio;

• gain regulatory acceptance for the development and commercialization of our product candidates and market success for ONPATPRO, 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 these objectives, we may not be able to develop product candidates, commercialize ONPATPRO or any future products, raise capital, expand our business or continue our operations.

The approach we are taking to discover and develop novel RNAi therapeutics may not lead to products that achieve market acceptance.

We have concentrated our efforts and therapeutic product research and development on RNAi technology and our future success depends on the successful development of this technology and products based on it. The scientific discoveries that form the basis for our efforts to discover and develop new drugs are relatively new. The scientific evidence to support the feasibility of developing drugs based on these discoveries is still limited. Skepticism as to the feasibility of developing RNAi therapeutics has been expressed in scientific literature. For example, there are potential challenges to achieving safe RNAi therapeutics based on the so-called off-target effects and activation of the interferon response. In addition, decisions by other companies with respect to their RNAi development efforts or their adoption of different or related technologies and the potential success of any such different or related technologies may increase skepticism in the marketplace regarding the potential for RNAi therapeutics.

Relatively few product candidates based on these discoveries have ever been tested in humans. We have spent and expect to continue to spend large amounts of money developing siRNAs that possess the properties typically required of drugs, and to date, we have received regulatory approval for one product. In addition, the compounds we are developing may not demonstrate in patients the chemical and pharmacological properties ascribed to them in laboratory studies, and they may interact with human biological systems in unforeseen, ineffective or harmful ways. For example, in October 2016, we discontinued development of revusiran, an investigational RNAi therapeutic that was in development for the treatment of patients with cardiomyopathy due to hATTR amyloidosis, due to safety concerns. We conducted a comprehensive evaluation of the revusiran data and 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. Although we received regulatory approval for ONPATTRO in the U.S. and EU, if we do not succeed in developing multiple products that gain regulatory approval and succeed in the marketplace, we may not become profitable and the value of our common stock could decline.

Further, our focus solely on RNAi technology for developing drugs, as opposed to multiple, more proven technologies for drug development, increases the risks associated with the ownership of our common stock. If we are not successful in developing and commercializing additional products using RNAi technology, we may be required to change the scope and direction of our product development activities. In that case, we may not be able to identify and implement successfully an alternative product development strategy.

#### Risks Related to Our Financial Results and Need for Financing

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

We have experienced significant operating losses since our inception. At March 31, 2019, we had an accumulated deficit of \$3.02 billion. Although we have launched ONPATTRO in the U.S. and several countries in Europe, and expect to launch in additional countries during 2019, we may never attain profitability or positive cash flow from operations. For the three months ended March 31, 2019, we recognized \$26.3 million in net product revenues from sales of ONPATTRO. We expect to continue to incur annual net operating losses over the next several years and will require substantial resources over the next several years as we expand our efforts to discover, develop and commercialize RNAi therapeutics. In addition to revenues derived from sales of ONPATTRO, and other product candidates that achieve regulatory approval, 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. We cannot be certain that we will be able to maintain our existing alliances or secure and maintain new alliances, or meet the obligations or achieve any milestones that we may be required to meet or achieve to receive payments. We anticipate that revenues derived from such sources will not be sufficient to make us consistently profitable.

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 be successful in a range of

challenging activities, including 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 succeed in these activities, and may never generate revenues that are significant enough to achieve profitability. 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.

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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 we believe they will 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. 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 decline.

We will require substantial additional funds to complete our research, development and commercialization activities and if additional funds are not available, we may need to critically limit, significantly scale back or cease our operations.

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 ONPATPRO or any other products that are approved for commercial sale. Because we cannot be certain of the length of time or activities associated with successful development of our product candidates, we are unable to estimate the actual funds we will require to develop and commercialize them.

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:

- our continued progress in demonstrating that siRNAs can be active as drugs and achieve desired clinical effects; progress in our research and development programs, 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;
  - our ability to maintain and establish additional collaborative arrangements and/or new business initiatives;
- 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 resources, time and cost required for the preparation, filing, prosecution, maintenance and enforcement of patent claims;
- the costs associated with legal activities, including litigation, arising in the course of our business activities and our ability to prevail in any such legal disputes; and
- the timing, receipt and amount of sales and royalties, if any, from ONPATPRO and our other potential products.

If our estimates, predictions and financial guidance relating to these factors are incorrect, we may need to modify our operating plan.

Even if our estimates are correct, we will be required to seek additional funding in the future and intend to do so through either collaborative arrangements, public or private equity offerings or debt financings, 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.

In April 2016, our subsidiary, Alnylam U.S., Inc., entered into an aggregate of \$150.0 million in term loan agreements related to the build out of our drug substance manufacturing facility. In December 2017, we repaid in full \$120.0 million outstanding under one such term loan agreement. We are the guarantor under the remaining term loan agreement, which matures in April 2021. Interest on the borrowings is calculated based on LIBOR plus 0.45 percent. During an event of default under the remaining agreement, the obligations under such agreement will bear interest at a

rate per annum equal to the interest rate then in effect plus two percent. The obligations under the term loan agreement are secured by cash collateral in an amount equal to, at any given time, at least 100 percent of the principal amount outstanding under such agreement at such time. The remaining agreement includes restrictive covenants that could limit our flexibility in conducting future business activities and further limit our ability to change the nature of our business and, in the event of insolvency, the lender would be paid before holders of equity securities received any distribution of corporate assets. If an event of default occurs, the interest rate would increase and the lender would be entitled to take various actions, including the acceleration of amounts due under the loan. Our ability to satisfy our obligations under this agreement and meet our debt service obligations will depend upon our future performance, which will be subject to financial, business and other factors affecting our operations, many of which are beyond our control.



In addition, the terms of any financing 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. For example, our investor agreement with Sanofi Genzyme provides Sanofi Genzyme with the right, subject to certain exceptions, generally to maintain its ownership position in us until Sanofi Genzyme owns less than 7.5 percent of our outstanding common stock. In accordance with the investor agreement, to date, Sanofi Genzyme has exercised its right to purchase an additional 344,448 shares of our common stock in connection with our acquisition of Sirna Therapeutics, Inc. in March 2014, an aggregate of 401,281 shares of our common stock based on its 2014 and 2015 annual compensation-related rights and an aggregate of 1,042,067 shares of our common stock in connection with our public offerings in January 2015 and May 2017. While the exercise of these rights by Sanofi Genzyme has provided us with an additional \$147.7 million in cash to date, these exercises caused dilution to our 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, delay the build-out of our global commercial infrastructure or undergo future reductions in our workforce or other corporate restructuring activities, and our ability to achieve our strategy for 2020 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.

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 non-GAAP research and development and selling, general and administrative expenses, and expectations for our cash, cash equivalents and marketable debt securities available for operations, which guidance is based on estimates and the judgment of management. If, for any reason, our expenses differ materially from our guidance or we utilize our cash more quickly than anticipated, we may have to adjust our publicly announced financial guidance. 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 debt securities is subject to risks which may cause losses and affect the liquidity of these investments.

At March 31, 2019, we had \$1.24 billion in cash, cash equivalents and marketable debt securities, excluding the \$44.8 million of restricted investments related to our cash collateral of \$30.0 million under our term loan agreement and \$14.8 million security deposit for 675 West Kendall Street, Cambridge, Massachusetts. 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.

The effect of comprehensive U.S. tax reform legislation on us, our subsidiaries and our affiliates, whether adverse or favorable, is uncertain.

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. For example, on December 22, 2017, the President of the United States signed into law the Tax Cuts and Jobs Act of 2017, or the TCJA. Among a number of significant changes to the current U.S. federal income tax rules, the TCJA reduced the marginal U.S. corporate income tax rate from 35 percent to 21 percent, introduced a capital investment deduction, limited the current deduction for net interest expense, limited the use of net operating losses to offset future taxable income, and made extensive changes in the way in which income earned outside the U.S. is taxed in the U.S. We disclosed the estimated impact of the TCJA in our annual report on Form 10-K that was filed with the SEC on February 15, 2018. As of December 31, 2018, our analysis of the impact of the TCJA was complete and there were no material changes to the provisional amount recorded at December 31, 2017.

### 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 sales and distribution capabilities and also have newly established capabilities for marketing, sales and market access, as well as limited capacity for drug development due to our growing pipeline of RNAi 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, we formed a broad strategic alliance with Sanofi Genzyme in 2014. In January 2018, we and Sanofi Genzyme amended our 2014 collaboration to provide that we would develop and commercialize ONPATTRO and vutrisiran globally and Sanofi Genzyme would develop and commercialize fitusiran globally. In April 2019, we and Sanofi Genzyme further amended our 2014 collaboration and agreed to conclude the research and option phase under the 2014 collaboration. The material collaboration terms for ONPATTRO, vutrisiran and fitusiran, as previously announced, will continue unchanged. With respect to our Cardio-Metabolic Disease pipeline, we intend to seek future strategic alliances for these programs, under which we may retain certain product development and commercialization rights, or we may structure as global alliances, as we did in our collaboration with MDCO 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. 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. We expect the Regeneron collaboration to become effective in the second quarter of 2019.

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) Sanofi Genzyme for the development and commercialization of fitusiran worldwide, (ii) MDCO for all future development and commercialization of inclisiran worldwide, and (iii) Regeneron, upon effectiveness of the collaboration, for the development and commercialization of all programs targeting eye diseases (subject to limited exceptions), and potentially other CNS and liver programs. 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.

We may not be successful in entering into future alliances on terms favorable to us due to various factors, including our ability to successfully demonstrate POC for our technology in humans, including our ESC+ GalNAc conjugate technology or our alternative conjugate approach for delivering CNS or ocular product candidates, 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, our decision in October 2016 to discontinue development of revusiran could make it more difficult for us to attract collaborators due to concerns around the safety and/or efficacy of our technology

platform or product candidates. In addition, our decision in September 2017 to temporarily suspend dosing in all ongoing fitusiran studies pending further review of a fatal thrombotic serious adverse event, or SAE, and agreement with regulatory authorities on a risk mitigation strategy could, notwithstanding the alignment reached with the FDA on a risk mitigation strategy in November 2017 and reinitiation of such studies, contribute to further concerns about the safety of our therapeutic candidates. Even if we do succeed in securing any 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 Sanofi Genzyme, MDCO, Vir and Regeneron. 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 to develop that 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 relating to the development and commercialization of inclisiran worldwide may be terminated by MDCO at any time upon four months' prior written notice. 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, 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 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 rely on third parties to conduct our clinical trials, and if they fail to fulfill their obligations, our development plans may be adversely affected.

We rely on independent clinical investigators, contract research organizations, or 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. 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, 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 revenues could be delayed.

We have limited manufacturing experience and resources and we must incur significant costs to develop this expertise and/or rely on third parties to manufacture our products.

We have limited manufacturing experience. In order to continue to commercialize ONPATTRO, continue to develop our current product candidates, apply for regulatory approvals and, if approved, commercialize future products, we will need to develop, contract for, or otherwise arrange for the necessary manufacturing capabilities. Historically, our internal manufacturing capabilities were limited to small-scale production of material for use in in vitro and in vivo experiments that is not required to be produced under current good manufacturing practice, or cGMP, standards. 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, in April 2016, we completed our purchase of a parcel of land in Norton, Massachusetts, where we are constructing a cGMP manufacturing facility for drug substance for clinical and commercial use.

We may manufacture limited quantities of clinical trial materials ourselves, but otherwise we currently rely on third parties to manufacture the drug substance and finished product we will require for any clinical trials that we initiate and to support the commercial launch of ONPATTRO and any of our other product candidates. There are a limited number of manufacturers that supply synthetic siRNAs. We currently rely on a limited number of contract manufacturing organizations, or CMOs, for our supply of synthetic siRNAs. For example, in July 2015, we amended our manufacturing services agreement with Agilent, to provide for Agilent to supply, subject to any conflicting obligations under our third-party agreements, a specified percentage of the active pharmaceutical ingredients required for certain of our product candidates in clinical development, as well as other products the parties may agree upon in the future. We currently rely on Agilent to supply the active pharmaceutical ingredient to support the commercial supply of ONPATTRO and in March 2018, we entered into a manufacturing services agreement with Agilent for such commercial supply. There are risks inherent in pharmaceutical manufacturing that could affect the ability of our CMOs, including Agilent, to meet our delivery time requirements or provide adequate amounts of material to meet our needs. Included in these risks are potential synthesis and purification failures and/or contamination during the manufacturing process, as well as other issues with the CMO's facility and ability to comply with the applicable manufacturing requirements, which could result in unusable product and cause delays in our manufacturing timelines 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 siRNA requirements, we will likely need to secure alternative suppliers of synthetic siRNAs and such alternative suppliers are limited and may 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 drug substance for clinical and commercial use.

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. 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 very 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. 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.



Given the limited number of suppliers for our delivery technology and drug substance, we developed cGMP capabilities and processes for the manufacture of patisiran formulated bulk drug product for late stage clinical use and commercial supply. During 2015, we scaled our cGMP manufacturing capacity for ONPATTRO and believe we have adequate resources to supply our commercial needs. In addition, as noted above, we are developing our own capabilities to manufacture drug substance for clinical and commercial use. In developing these manufacturing capabilities by building our own manufacturing facilities, we have incurred substantial expenditures, and expect to incur significant additional expenditures in the future. In addition, the construction and qualification of our drug substance facility is a lengthy process to complete and there are many risks inherent in the construction of a new facility that could result in delays and additional costs, including the need to obtain access to necessary equipment and third-party technology, if any. Also, we have had to, and will likely need to continue to, hire and train qualified employees to staff our facilities. We do not currently have a second source of supply for patisiran formulated bulk drug product. 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 of patisiran formulated bulk drug product and drug substance, 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. Any delay or setback in the manufacture of ONPATTRO could impede ongoing commercial supply, which could significantly impact our revenues and operating results.

The manufacturing process for ONPATTRO 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. 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. We may experience difficulty in obtaining adequate manufacturing capacity for our needs and the needs of our collaborators, who we have, in some instances, the obligation to supply. If we are unable to obtain or maintain CMOs for our product candidates, or to do so on commercially reasonable terms, we may not be able to successfully develop and commercialize our products.

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, including Agilent, 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 Agilent or any other 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 commercial demands for our products.

If any CMO with whom we contract, including Agilent, fails to perform its obligations, we may be forced to manufacture the materials ourselves, for which we may not have the capabilities or resources, or enter into an agreement with a different CMO, which we may not be able to do on reasonable terms, if at all. In either scenario, our clinical trials or commercial distribution could be delayed significantly as we establish alternative supply sources. In some cases, the technical skills required to manufacture our products or product candidates may be unique or proprietary to the original CMO and we may have difficulty, or there may be contractual restrictions prohibiting us from, transferring such skills to a back-up or alternate supplier, or we may be unable to transfer such skills at all. In

addition, if we are required to change CMOs for any reason, we will be required to verify that the new CMO maintains facilities and procedures that comply with quality standards and with all applicable regulations and guidelines. We will also need to verify, such as through a manufacturing comparability study, that any new manufacturing process will produce our product according to the specifications previously submitted to or approved by the FDA or another regulatory authority. The delays associated with the verification of a new CMO could negatively affect our ability to develop product candidates or commercialize our products in a timely manner or within budget. Furthermore, a CMO may possess technology related to the manufacture of our product candidate that such CMO owns independently. This would increase our reliance on such CMO or require us to obtain a license from such CMO in order to have another CMO manufacture our products or product candidates.

We have limited sales and distribution experience and newly established capabilities for marketing, sales and market access, and expect to continue to invest significant financial and management resources to continue to build these capabilities and to establish a global commercial infrastructure.

We have limited sales and distribution experience and newly established capabilities for marketing, sales and market access. We currently expect to rely heavily on third parties to launch and market certain of our product candidates in certain geographies, if approved. However, as a result of the January 2018 amendment to our Sanofi Genzyme collaboration, we intend to commercialize ONPATTRO, as well as several of our late-stage product candidates if approved, including givosiran, lumasiran and vutrisiran, on our own globally. Accordingly, we have developed internal sales, distribution and marketing capabilities as part of our core product strategy initially in the U.S. and the EU, and with expansion ongoing in Canada, Switzerland, Central and Eastern Europe, Japan, Brazil and eventually in other major markets in the rest of the world, which will require significant financial and management resources. For those products for which we will perform sales, marketing and distribution functions ourselves, including ONPATTRO and, if approved, givosiran, lumasiran and vutrisiran, 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:

- we may not be able to attract and build a significant marketing or sales force;
  - we may not be able to establish our global capabilities and infrastructure in a timely manner;
- the cost of establishing a marketing or sales force 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 sales, marketing and distribution capabilities for ONPATTRO and any future products, we will not be able to successfully commercialize our products without reliance on third parties.

Credit and financial market conditions may exacerbate certain risks affecting our business from time to time.

Due to tightening of global credit, there may be a disruption or delay in the performance of our third-party contractors, suppliers or collaborators. We rely on third parties for several important aspects of our business, including significant portions of our manufacturing needs, development of product candidates and conduct of clinical trials. If such third parties are unable to satisfy their commitments to us, our business could be adversely affected.

Our ability to secure additional financing in addition to our term loan agreement and to satisfy our financial obligations under indebtedness outstanding from time to time will depend upon our future operating performance, which is subject to then prevailing general economic and credit market conditions, including interest rate levels and the availability of credit generally, and financial, business and other factors, many of which are beyond our control. In light of periodic uncertainty in the capital and credit markets, there can be no assurance that sufficient financing will be available on desirable or even any terms to fund investments, acquisitions, stock repurchases, dividends, debt refinancing or extraordinary actions.

#### 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 and medical staff. The loss of the service of any of the members of our senior management, including Dr. John Maraganore, our Chief Executive Officer, may significantly delay or prevent the achievement of product development and commercialization, and other business objectives. Our employment arrangements with our key personnel are terminable without notice. We do not

carry key person life insurance on any of our employees.

We have grown our workforce significantly over the past several years and anticipate continuing to add a significant number of additional employees as we focus on achieving our Alnylam 2020 strategy. 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, due to the risks associated with developing a new class of medicine, we may experience disappointing results in a clinical program and our stock price may decline as a result, as was the case following our decision in October 2016 to discontinue our revusiran program, and, to less of an extent, following our temporary suspension of dosing in our fitusiran program in September 2017. As a result, we may face additional challenges in attracting and retaining employees. In addition, we may not be successful commercializing our first product and as a result, we may be unable to attract and retain highly qualified sales and marketing professionals to support ONPATTRO 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 plan.

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We may have difficulty expanding our operations successfully as we evolve 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 launch of ONPATTRO and increase the number of product candidates we are developing, we will also need to expand our operations in the U.S. and continue to build operations in the EU and other geographies, including Japan and Latin America. In August 2018, we received regulatory approval for ONPATTRO in the U.S. and EU, and as a result of the January 2018 amendment to our Sanofi Genzyme collaboration, we now have global development and commercialization rights for ONPATTRO. We also filed for regulatory approvals in Canada, Japan and Switzerland, and plan to file for additional regulatory approvals in additional countries throughout 2019.

As noted above, we grew our workforce significantly from 2016 through 2018, and anticipate continuing to hire additional employees in 2019, including employees in the EU, Japan and other territories, as we focus on the commercialization of ONPATTRO and achieving our Alnylam 2020 strategy. This expected growth is placing a strain on our administrative and operational infrastructure, and 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 operations in the U.S., the EU, Japan 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 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 expand due to our development progress, we will need to continue to manage additional relationships with various collaborators, suppliers and other organizations. Our ability to manage our operations and future growth will require us to continue to improve our operational, financial and management controls and systems, reporting systems and infrastructure, and policies and procedures. We may not be able to implement improvements to our management information and control systems in an efficient or timely manner and may discover deficiencies in existing systems and controls.

The increasing use of social media platforms presents new risks and challenges.

Social media is increasingly 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 ONPATTRO 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 relating to such use are not always clear. This evolution creates uncertainty and risk of noncompliance with regulations applicable to our business, resulting in potential regulatory actions against us. For example, 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 we fail to monitor and comply with applicable AE reporting obligations or 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 social networking website. 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 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.

Despite the implementation of security measures, our internal computer systems and those of our contractors and consultants are vulnerable to damage from computer viruses, unauthorized or inappropriate access or use, natural disasters, terrorism, war, 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.

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

In June 2016, the United Kingdom, or UK, held a referendum in which voters approved an exit from the EU, commonly referred to as "Brexit." This referendum has created political and economic uncertainty, particularly in the UK and the EU, and this uncertainty may persist for years. A withdrawal could, among other outcomes, disrupt the free movement of goods, services and people between the UK and the EU, and result in increased legal and regulatory complexities, as well as potential higher costs of conducting business in Europe. The UK's vote to exit the EU could also result in similar referendums or votes in other European countries in which we do business. Given the lack of comparable precedent, it is unclear what financial, trade and legal implications the withdrawal of the UK from the EU would have and how such withdrawal would affect us.

For example, Brexit could result in the UK or the EU significantly altering its regulations affecting the clearance or approval of our product candidates that are developed in the UK. Any new regulations could add time and expense to the conduct of our business, as well as the process by which our products receive regulatory approval in the UK, the EU and elsewhere. In addition, the announcement of Brexit and the withdrawal of the UK from the EU have had and may continue to have a material adverse effect on global economic conditions and the stability of global financial markets, and may significantly reduce global market liquidity and restrict the ability of key market participants to operate in certain financial markets. Any of these effects of Brexit, among others, could adversely affect our business, our results of operations, liquidity and financial condition.

## Risks Related to Our Industry

### Risks Related to Development, Clinical Testing and Regulatory Approval of Our Product Candidates

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. For example, in October 2016, we discontinued development of one of our product candidates, which included a Phase 3 clinical trial. We currently have multiple other programs in clinical development, including several internal programs and two partnered programs currently in Phase 3 development, as well as several earlier stage clinical programs. In April 2019, we reported positive complete results from our ENVISION Phase 3 clinical trial for givosiran, an investigational RNAi therapeutic targeting ALAS1 in development for the treatment of AHP, and we expect to file an NDA and an MAA in mid-2019. However, we may not be able to further advance this or any other product candidate through clinical trials and regulatory approval.

If we enter into clinical trials, the results from nonclinical testing or early 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. 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 could have a material adverse effect on our business and operating results. Moreover, ONPATTRO and our current product candidates, including givosiran, lumasiran, vutrisiran, fitusiran and inclisiran, each employ novel delivery technologies that 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. For example, in October 2016, we announced our decision to discontinue development of revusiran, an investigational RNAi therapeutic that was being developed for the treatment of patients with cardiomyopathy due to hATTR amyloidosis. Our decision followed the recommendation of the revusiran ENDEAVOUR Phase 3 study Data Monitoring Committee, or DMC, to suspend dosing and the observation of an imbalance in mortality in revusiran-treated patients as compared to those on placebo. We conducted a comprehensive evaluation of the revusiran data and reported the results of our evaluation in August 2017. Following our evaluation, we continue to believe that the decision to discontinue development of revusiran does not affect ONPATTRO or any of our other investigational RNAi therapeutic programs in development. 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. In December 2017, we reached alignment with study investigators and the FDA on safety measures and a risk mitigation strategy to enable resumption of dosing in clinical studies with fitusiran, including our Phase 2 open-label extension, or OLE, study, and the ATLAS Phase 3 program, including protocol-specified guidelines and additional investigator and patient education concerning reduced doses of replacement factor or bypassing agent to treat any breakthrough bleeds in fitusiran studies.



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. Moreover, given the temporary suspension of dosing in our fitusiran studies in September 2017 due to a fatal thrombotic SAE, people with hemophilia may be more reluctant to enroll in the ATLAS Phase 3 program of fitusiran. 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 now intend to focus our cemdisiran clinical development efforts in a different indication. Delays or difficulties in patient enrollment or difficulties retaining trial participants, including as a result of the availability of existing or other investigational treatments or safety concerns, 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, as noted above, in September 2017, we announced that we had temporarily suspended dosing in all ongoing fitusiran studies pending further review of a fatal thrombotic SAE that occurred in a patient with hemophilia A without inhibitors who was receiving fitusiran in our Phase 2 OLE study. In addition, in October 2016, we made the decision to discontinue our revusiran program. Following reports in the revusiran Phase 2 OLE study of new onset or worsening peripheral neuropathy, the revusiran ENDEAVOUR Phase 3 study DMC assembled in early October 2016 at our request to review these reports and ENDEAVOUR safety data on an unblinded basis. The DMC did not find conclusive evidence for a drug-related neuropathy signal in the ENDEAVOUR trial, but informed us that the benefit-risk profile for revusiran no longer supported continued dosing. We subsequently reviewed unblinded ENDEAVOUR data which revealed an imbalance of mortality in the revusiran arm as compared to placebo. Further, a review by us in 2017 of the ENDEAVOUR results subsequent to the completion of follow-up of the patients post-dosing discontinuation revealed an imbalance in new onset or worsening peripheral neuropathy in the revusiran arm as compared to placebo. We had previously reported, in July 2016, preliminary data from our revusiran Phase 2 OLE study for 12 patients who had reached the 12-month endpoint as of the data transfer date of May 26, 2016. SAEs were observed in 14 patients, one of which, a case of lactic acidosis, was deemed possibly related to the study drug and the patient discontinued treatment. There were a total of seven deaths reported at that time in the revusiran OLE study, all of which were unrelated to the study drug. The majority of the AEs were mild or moderate in severity; injection site reactions, or ISRs, were reported in 12 patients. In August 2015, we reported that three patients had discontinued from the revusiran Phase 2 OLE study due to recurrent localized reactions at the injection site or a diffuse rash; no further discontinuations due to ISRs had occurred as of May 26, 2016.

In our ENVISION Phase 3 study of givosiran in patients with AHP, AEs were reported in 89.6 percent of givosiran patients and 80.4 percent of placebo patients; SAEs were reported in 20.8 percent of givosiran patients and 8.7 percent of placebo patients. Of the SAEs reported in givosiran patients, there were two cases of chronic kidney disease, or CKD, and one case each of asthma, device-related infection, gastroenteritis, hypoglycemia, abnormal liver function test, major depression, pain management and pyrexia. Three SAEs in givosiran patients were reported as related to study drug: pyrexia, abnormal liver function test and CKD. The two SAEs of CKD noted above were considered serious due to elective hospitalization for diagnostic evaluation. There were no deaths in the study. One patient in the givosiran arm discontinued treatment due to an increase in alanine aminotransferase, or ALT, level greater than eight times the upper limit of normal, a protocol-defined stopping rule. The increase in ALT levels subsequently resolved. AEs reported in greater than 10 percent of givosiran patients and seen more frequently compared to placebo were

nausea, ISRs, CKD, and fatigue. Four of five of the patients with AEs reported as CKD had a prior history of CKD or a baseline estimated glomerular filtration rate less than 60 mL/min/1.73m<sup>2</sup>. No patients had clinically significant proteinuria and there were no treatment discontinuations due to renal AEs.

In our ALN-VSP clinical trial, one patient with advanced pancreatic neuroendocrine cancer with extensive involvement of the liver developed hepatic failure five days following the second dose of ALN-VSP and subsequently died; this was deemed possibly related to the study drug. As demonstrated by the discontinuation of our revusiran program in October 2016 and the temporary suspension of dosing in September 2017 in our fitusiran studies, the occurrence of SAEs and/or AEs can result in the suspension or termination of clinical trials of a product candidate by us 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;
- 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;
- 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 may be unable to obtain U.S. or foreign regulatory approval and, as a result, unable to commercialize our product candidates.

Our 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 are developing will not obtain the regulatory approvals necessary for us or our collaborators to begin selling them.

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We have limited experience in conducting and managing the clinical trials necessary to obtain regulatory approvals, including approval by the FDA. 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 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 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 may submit. Moreover, the FDA may respond to these submissions by defining requirements we may not have anticipated. Such responses could lead to significant delays in the development of our product candidates. In addition, because there may be approved treatments for some of the diseases for which we may seek approval, or treatments in development which are approved by the time we apply for approval, in order to receive regulatory approval, we 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.

Any delay or failure in obtaining required approvals for our product candidates could have a material adverse effect on our ability to generate revenues from any product candidate for which we may seek approval in the future. Furthermore, any regulatory approval to market any product may be subject to limitations on the approved uses for which we 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 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 ONPATPRO, which was approved in the U.S. and EU in August 2018, 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 ONPATTRO or other drug products required as a condition of approval or agreed to by us. The regulatory approvals that we receive for ONPATTRO, as well as any regulatory approvals we receive for any other product candidates, including givosiran, may also be subject to limitations on the approved uses for which the product may be marketed. 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 ONPATTRO is 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 ONPATTRO may be more modest than originally anticipated;
- regulatory approvals for ONPATTRO 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 ONPATTRO, increase our expenses and impair our ability to successfully commercialize ONPATTRO.

The CMO and manufacturing facilities we use to make ONPATTRO and certain of our current product candidates, including our Cambridge facility, our future Norton facility, and 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, the EMA and potentially other regulatory authorities in connection with the review of our NDA and MAA for ONPATTRO, and may be subject to similar inspection in connection with any subsequent applications for regulatory approval of ONPATTRO 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. We have developed cGMP capabilities and processes for the manufacture of patisiran formulated bulk drug product for commercial use. In addition, in April 2016, we completed our purchase of a parcel of land in Norton, Massachusetts, where we are constructing a cGMP manufacturing facility for drug substance for clinical and 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 these materials 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.

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 will 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;

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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, ONPATTRO utilizes an intravenous mode of administration with pre-medication that physicians and/or patients may not readily adopt, or which may not compete with other available options, including inotersen, marketed by Akcea Therapeutics Inc., or Akcea, which is administered subcutaneously, or tafamidis, marketed in certain countries outside of the U.S. by Pfizer and reportedly available within the U.S. as part of an early access program, 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.

In addition, our estimates regarding the potential market size for ONPATTRO, or any future products at the time we commence commercialization, may be materially different from what we expect, 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 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 data from the exploratory cardiac endpoints included in our APOLLO Phase 3 study. This could have an adverse impact on the market opportunity for ONPATTRO in the U.S.

We may incur significant liability if enforcement authorities allege or determine that we are engaging in commercial activities or promoting ONPATTRO in a way that violates applicable regulations.

Physicians have the discretion to prescribe 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 do not regulate a physician's 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. Manufacturers may not promote drugs for off-label uses. Accordingly, we may not promote ONPATTRO 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. A company that is found to have improperly promoted off-label uses may be subject to significant liability, which may include civil and administrative remedies as well as criminal sanctions.

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. We intend to engage in medical education activities and communicate with healthcare providers in compliance with all applicable laws and regulatory guidance.

In addition, we offer patient support services to assist patients receiving treatment with ONPATTRO. 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 False Claims Act, or FCA, face significant liability, including civil and administrative penalties, criminal sanctions, and potential exclusion from participation in government programs. We have designed our programs in a manner that we believe complies with all applicable laws and regulations and have implemented a robust compliance program to support compliance with such laws.

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 from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, to induce either the referral of an individual for a healthcare item or service, or the purchasing or ordering of an item or service, for which payment may be made under a federal healthcare program such as Medicare or Medicaid.

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•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 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.

•The U.S. federal Open Payments requirements were implemented by the Centers for Medicare and Medicaid Services, or CMS, pursuant to the Patient Protections and Affordable Care Act, or ACA. Under the Open Payments Program, manufacturers of medical devices, medical supplies, biological products and drugs covered by Medicare, Medicaid and the Children’s Health Insurance Programs must report all transfers of value, including consulting fees, travel reimbursements, research grants, and other payments or gifts with values over \$10 made to physicians and teaching hospitals as well as ownership and investment interests held by physicians and their immediate family members.

•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 GDPR, and the e-Privacy Directive (2002/58/EC), and the national laws implementing each of them, as well as 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.

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

In the EU, the GDPR replaced the EU Data Protection Directive on May 25, 2018. The GDPR introduced new data protection requirements in the EU, as well as potential fines for noncompliance of up to the greater of €20,000,000 or four percent of total annual global revenue. The regulation imposes numerous new requirements for the collection, use

and disclosure of personal information, including: more stringent requirements relating to data subject consent; what information must be shared with data subjects regarding how their personal information is used; the obligation to notify regulators and affected individuals of personal data breaches; extensive new internal privacy governance obligations; and obligations to honor expanded rights of individuals in relation to their personal information (e.g., the right to access, correct and delete their data). In addition, the GDPR maintains the EU Data Protection Directive's restrictions on cross-border data transfer. The GDPR increases the responsibility and liability of pharmaceutical companies in relation to processing personal data, and companies may be required to put in place additional mechanisms to ensure compliance with the new EU data protection rules. Further, Brexit has created uncertainty with regard to the status of the UK as an "adequate country" for the purposes of data transfers outside the European Economic Area, or EEA. In particular, it is unclear how data transfers to and from the UK will be regulated. These changes may require us to find alternative bases for the compliant transfer of personal data from the UK to the U.S., and we are monitoring developments in this area.

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, 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 are continuing to establish our global compliance infrastructure following the launch of ONPATTRO in August 2018 in the U.S. and in October 2018 in the EU and as we prepare for the launch in additional countries, including Japan, Switzerland and Canada, 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. 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 ONPATTRO, 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;
- 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.

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 ONPATTRO in the U.S. and EU 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 obtain regulatory approval for a product, including ONPATTRO, in a particular country, but then be subject to price regulations 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 ONPATTRO 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. ONPATTRO 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 ONPATTRO or any future products on a competitive basis. Increasingly, the third-party payors who pay for or 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 ten value-based agreements and are negotiating additional value-based agreements for ONPATTRO with certain private health insurers. The goal of these agreements is to ensure that we are paid based on the ability of ONPATTRO to deliver results in the real world setting comparable to those demonstrated in clinical trials. Partnering with payers on these agreements is intended to provide more certainty to them for their investment, and help accelerate coverage decisions for patients. The agreements are structured to link ONPATTRO's performance in real-world use to financial terms. If the price we are able to charge for ONPATTRO or any other products we develop, 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 2.2 percent 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.

We currently expect that some of the drugs we develop may need to be administered under the supervision of a physician or other healthcare professional on an outpatient basis, including ONPATTRO. 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. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement rates. Our inability to promptly obtain coverage or adequate reimbursement rates from both government-funded and private payors for ONPATTRO or other new drugs that we develop and for which we obtain regulatory approval could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products, and our overall financial condition.

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. 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 have included prescription drug benefit legislation that was enacted in 2003 and

took effect in January 2006, healthcare reform legislation enacted by certain states, and major healthcare reform legislation that was passed by Congress and enacted into law in the U.S. in 2010. These developments could, directly or indirectly, affect our ability to sell ONPATTRO or future products, if approved, at a favorable price.

In particular, in March 2010, 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.

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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 percent 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 two percent per fiscal year, which went into effect in April 2013 and will remain in effect through 2027 unless additional Congressional action is taken. 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 ONPATTRO or any of our product candidates for which we may obtain regulatory approval or the frequency with which ONPATTRO or any future product is prescribed or used.

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 the 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.

Members of Congress and the Trump administration have expressed an intent to pass legislation or adopt executive orders to fundamentally change or repeal parts of the ACA. While Congress has not passed repeal legislation to date, the TCJA includes a provision repealing the individual insurance coverage mandate included in ACA, effective January 1, 2019. Further, on January 20, 2017, an Executive Order was signed directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of

any provision of the ACA that would impose a fiscal burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On October 13, 2017, an Executive Order was signed terminating the cost-sharing subsidies that reimburse insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. Further, on June 14, 2018 the United States Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than \$12.0 billion in ACA risk corridor payments to third-party

payors. The effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace, providers, and our business, are not yet known. In addition, CMS has recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. The Bipartisan Budget Act of 2018, or the BBA, among other things, amends the ACA effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the “donut hole.” In July 2018, the CMS published a final rule permitting further collections and payments to and from certain ACA qualified health plans and health insurance issuers under the ACA risk adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. Moreover, CMS issued a final rule in 2018 that will give states greater flexibility, starting in 2020, in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. On December 14, 2018, a U.S. District Court Judge in the Northern District of Texas, or the Texas District Court Judge, ruled that the individual mandate is a critical and inseparable feature of the ACA, and therefore, because it was repealed as part of the TCJA, the remaining provisions of the ACA are invalid as well. While the Texas District Court Judge issued an order staying the judgment pending appeal in December 2018, and both the Trump Administration and CMS have stated the ruling will have no immediate impact, it is unclear how this decision, subsequent appeals and other efforts to repeal and replace the ACA will impact the ACA and our business. Congress may consider other legislation to replace elements of the ACA. The implications of the ACA, its possible repeal, any legislation that may be proposed to replace the ACA, or the political uncertainty surrounding any repeal or replacement legislation for our business and financial condition, if any, are not yet clear.

The costs of prescription pharmaceuticals in the U.S. has also been the subject of considerable discussion in the U.S., and members of Congress and the Trump administration have stated that they will address such costs through new legislative and administrative measures. To date, there have been several U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. At the federal level, Congress and the Trump administration have each indicated that it will continue to pursue new legislative and/or administrative measures to control drug costs. The Trump administration released a “Blueprint,” or plan, to reduce the cost of drugs. The Trump administration’s Blueprint contains certain measures that the U.S. Department of Health and Human Services is already working to implement. For example, on October 25, 2018, CMS issued an Advanced Notice of Proposed Rulemaking, or ANPRM, indicating it is considering issuing a proposed rule in the spring of 2019 on a model called the International Pricing Index. This model would utilize a basket of other countries’ prices as a reference for the Medicare program to use in reimbursing for drugs covered under Part B. The ANPRM also included an updated version of the Competitive Acquisition Program, as an alternative to current “buy and bill” payment methods for Part B drugs. Such a proposed rule could limit our product pricing and have material adverse effects on our business.

Individual state legislatures have become increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological 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 health care 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 health care 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 ONPATTRO 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.

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

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, 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. 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 ONPATTRO or any future products in those countries would be negatively affected.

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 EU. Further, GDPR provides a broad right for EU 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. GDPR grants individuals the opportunity to object to the processing of their personal information, allows them to request deletion of personal information in certain circumstances, and provides the individual with an express right to seek legal remedy in the event the individual believes his or her rights have been violated. Further, the GDPR imposes strict rules on the transfer of personal data out of the EU to the U.S. or other regions that have not been deemed to offer “adequate” privacy protections.

Failure to comply with the requirements of the GDPR and the related national data protection laws of the EU Member States, which may deviate slightly from the GDPR, may result in fines of up to four percent of total global annual revenue, or €20,000,000, whichever is greater, and in addition to such fines, we may be the subject of litigation and/or adverse publicity, which could have material adverse effect on our reputation and business. As a result of the implementation of the GDPR, we are required to put in place additional mechanisms to ensure compliance with the new data protection rules. For example, the GDPR requires us to make more detailed disclosures to data subjects, requires disclosure of the legal basis on which we can process personal data, may make it harder for us to obtain valid consent for processing, will require the appointment of 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 EU, imposes additional obligations on us when we are contracting with service providers and requires us to adopt appropriate privacy governance including policies, procedures, training and data audit.

We are subject to the supervision of local data protection authorities in those jurisdictions where we are monitoring the behavior of individuals in the EU (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 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. The draft ePrivacy Regulation imposes strict opt-in marketing rules with limited exceptions for business-to-business communications, alters rules on third-party cookies, web beacons and similar technology and significantly increases

potential fines to the same levels as GDPR (i.e., the greater of €20,000,000 or four percent of total global annual revenue). 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 and commentators now expect it to be adopted during the middle or second half of 2020.

There is significant uncertainty related to the manner in which data protection authorities will seek to enforce compliance with GDPR. Further, Brexit has created uncertainty with regard to the status of the UK as an 'adequate country' for the purposes of data transfers outside the EEA. In particular, it is unclear how data transfers to and from the UK will be regulated. Enforcement uncertainty and the costs associated with ensuring GDPR and e-Privacy compliance may be onerous and may adversely affect our business, financial condition, results of operations and prospects.

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 two percent 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 BBA, these reductions will stay in effect through 2027 unless additional Congressional action is taken. 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 ONPATTRO and any other products we may develop.

In addition, in the case of any U.S. federal government shutdown, now or in the future, that continued for a prolonged period of time, FDA review and approval processes, and FDA interactions during clinical development, could be delayed. Resolving such delays could force us or our collaborators to incur significant costs, could limit our allowed activities or the allowed activities of our collaborators, could diminish any competitive advantages that we or our collaborators may attain or could adversely affect our business, financial condition, results of operations and prospects, the value of our common stock and our ability to bring new products to market as forecasted. Even without such delay, there is no guarantee we will receive approval for our product candidates on a timely basis, or at all.

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. If we succeed in marketing products, including ONPATTRO, product liability claims could result in an FDA investigation of the safety and effectiveness of our 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 ONPATTRO. 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.



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 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 facilities comply with the relevant guidelines of the City of Cambridge, 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 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 technology 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 may be required to obtain licenses under third-party patents to market ONPATTRO or future products or conduct our research and development or other activities. If licenses are not available to us on acceptable terms, we 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 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 America Invents Act, 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, Cancer Research Technology Limited, Ionis Pharmaceuticals, Inc., or Ionis, the Massachusetts Institute of Technology, or MIT, Whitehead Institute for Biomedical Research, or Whitehead, Max Planck Innovation GmbH (formerly known as Garching Innovation GmbH), or Max Planck, and Arbutus Biopharma Corporation, or Arbutus (formerly Tekmira Pharmaceuticals Corporation). 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 America Invents Act, which became available to third party challengers on September 16, 2012, in various patent offices relating to patent rights in the RNAi field. For example, various third parties have initiated oppositions to patents in our McSwiggen, Kreutzer-Limmer and Tuschl II series in the EPO and in other jurisdictions. 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. In addition, third parties may attempt to invalidate our intellectual property rights. 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 therapeutic candidates or marketed products, including ONPATTRO. 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, including ONPATTRO. 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, 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 patent litigation or other proceedings related to a determination of rights, we could incur substantial costs and expenses, 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. Likewise, 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. We and Dicerna settled the ongoing litigation between us in April 2018 and 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. For example, in March 2011, Arbutus filed a civil complaint against us alleging, among other things, misappropriation of its confidential and proprietary information and trade secrets. In November 2012, we settled this litigation and restructured our contractual relationship with Arbutus. In connection with this restructuring, we incurred a \$65.0 million charge to operating expenses during the fourth quarter of 2012.

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.

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 Arbutus and 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.

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 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 require us to stop the infringing activity or obtain a license. Any license required under any patent may not be made available on commercially acceptable 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 ONPATTRO 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 is 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 Genzyme and the related Exclusive TTR License and AT3 License Terms. Ionis claims it is owed technology access fees based on rights granted and amounts paid to us in connection with the Sanofi Genzyme restructuring. In November 2018, we received notice that Ionis had filed a Demand for Arbitration with the Boston office of the American Arbitration Association against us, asserting, among other things, breach of contract. In December 2018, we filed our answer to Ionis's Demand for Arbitration, denying any liability to Ionis and the matter is currently in the discovery phase. The arbitration has been set for a five-day hearing beginning on February 3, 2020. While we dispute that additional technology access fees are owed to Ionis, there can be no assurance that we will resolve this matter favorably or that it will not have a material adverse impact on our future results of operations.

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 ONPATTRO 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 ONPATTRO or other products that we successfully develop and commercialize, if any. 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, 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. 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. For example, we developed ONPATTRO 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 authorisation 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, marketed by Pfizer in Europe and certain countries outside the U.S., and inotersen, developed by Ionis and licensed to Akcea, which is now approved in the U.S., the EU and Canada, as well as product candidates in various stages of clinical development, including an additional investigational drug being developed by Ionis. In addition, in August 2018, Pfizer announced the primary results from a Phase 3 study of tafamidis in patients with TTR cardiomyopathy. In June 2017 and May 2018, respectively, the FDA granted Fast Track and Breakthrough Therapy designations for tafamidis for TTR amyloid cardiomyopathy. In March 2018, the Ministry of Labor Health and Welfare in Japan granted SAKIGAKE designation to tafamidis for this indication and in March 2019, Pfizer announced the additions of wild-type and mutant indications in Japan for TTR amyloid cardiomyopathy. Finally, we are aware that Eidos Therapeutics, Inc., or Eidos, initiated a Phase 3 clinical trial of AG10, a TTR stabilizer, in ATTR-CM in February 2019. Eidos also plans to initiate a Phase 3 clinical trial of AG10 in ATTR-PN patients in the first half of 2019. While we believe that ONPATTRO will have a competitive product profile, it is possible it will not compete favorably with these products and product candidates, or others, and, as a result, may not achieve commercial success. Moreover, positive data and/or the commercial success of competitive products could negatively impact our stock price.

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.

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We are aware of product candidates in various stages of clinical development for the treatment of PH1 which would compete with lumasiran, our investigational RNAi therapeutic now in Phase 3 studies for the treatment of this disease, including Oxabact<sup>®</sup>, a bacteria-based investigational therapy in Phase 3 development by Oxthera AB, relaxalase an investigational enzyme therapy in Phase 2 development for primary or severe secondary hyperoxaluria by Allena Pharmaceuticals, and DCR-PHXC, an investigational RNAi therapeutic in development by Dicerna for the treatment of primary hyperoxaluria. In March 2019, Dicerna announced the initiation of screening for a pivotal study of DCR-PHXC for this indication. 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, or Takeda, Marina Biotech, Inc., Arrowhead Research Corporation, or Arrowhead, and its subsidiary, Calando Pharmaceuticals Inc., or Calando, Quark Pharmaceuticals, Inc., or Quark, Silence, Arbutus, Sylentis S.A.U., Dicerna, 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, Arrowhead, and its subsidiary, Calando, 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 Pharma AG, has obtained specific exclusive licenses for 30 gene targets, that include access to certain aspects of our technology that give them the right to compete with us in certain circumstances. 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 has received marketing approval for an antisense drug, inotersen that was developed by Ionis, in the U.S., the EU and Canada, for the treatment of 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 is more advanced than that of RNAi therapeutics, 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. 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. For example, in October 2016, we announced that we were discontinuing the development of revusiran and our stock price declined significantly as a result and in September 2017, following our temporary suspension of dosing in our fitusiran program, our stock also declined, although to a lesser extent. 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, a class action complaint was filed on September 26, 2018 in the United States District Court for the Southern District of New York, entitled Caryl Hull Leavitt v. Alnylam Pharmaceuticals, Inc., et. al., Case No. 18-CV-8845. The complaint alleges that we and our Chief Executive Officer and our Chief Financial Officer violated certain federal securities laws, specifically under Sections 10(b) and 20(a) of the Exchange Act, and Rule 10b-5 promulgated thereunder. The plaintiff seeks unspecified damages on behalf of a purported class of purchasers of our common stock between February 15, 2018 and September 12, 2018. We believe that the allegations contained in the complaint are without merit and intend to defend the case vigorously. However, whether or not the plaintiff's claims are successful, this type of litigation is often expensive and diverts management's attention and resources, which could adversely affect the operation of our business. If we are ultimately required to pay significant defense costs, damages or settlement amounts, such payments could adversely affect our operations.

We may be the target of similar litigation in the future. Any 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 this or any other litigation exceed our insurance coverage, we may be forced to bear some or all of these costs and expenses directly, which could be substantial.

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 March 31, 2019, our five largest stockholders beneficially owned in excess of 50 percent of our outstanding shares of common stock. As of January 17, 2019, Sanofi Genzyme beneficially owned 10,554,134 shares of our common stock, representing approximately 9.9 percent of the shares of common stock then outstanding. In April 2019, in connection

with the end of the research and option phase of the Sanofi Genzyme collaboration, we agreed to release Sanofi Genzyme from the lock-up restrictions under the existing investor agreement. Sanofi Genzyme is permitted to sell shares of our common stock in transactions approved by us or in fully bought block sale transactions satisfying the conditions set forth in the amended and restated investor agreement. If Sanofi Genzyme, our other 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, including Sanofi Genzyme, also 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.

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

As of January 17, 2019, Sanofi Genzyme held 10,554,134 shares of our common stock, or approximately 9.9% of our outstanding common stock. Sanofi Genzyme has the right to increase its ownership to up to 30 percent. In addition, as of closing of the stock purchase in connection with the 2019 Regeneron collaboration, which is expected in the second quarter of 2019, Regeneron will hold approximately 4% of our outstanding common stock and will have the right to increase its ownership up to 30 percent. This concentration of ownership may harm the market price of our common stock 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 percent 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 percent 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.

## ITEM 6. EXHIBITS.

10.1\*# Amended and Restated 2004 Employee Stock Purchase Plan, as amended.

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 The following materials from the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2019, formatted in XBRL (Extensible Business Reporting Language): (i) the Condensed Consolidated Balance Sheets, (ii) the Condensed Consolidated Statements of Comprehensive Loss, (iii) the Condensed Consolidated Statements of Cash Flows, and (iv) Notes to Condensed Consolidated Financial Statements.

\*Management contracts or compensatory plans or arrangements.

#Filed herewith.



SIGNATURES

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

ALNYLAM PHARMACEUTICALS, INC.

Date: May 2, 2019 /s/ John M. Maraganore  
John M. Maraganore, Ph.D.  
Chief Executive Officer  
(Principal Executive Officer)

Date: May 2, 2019 /s/ Manmeet S. Soni  
Manmeet S. Soni  
Senior Vice President, Chief Financial Officer  
(Principal Financial and Accounting Officer)