ALNYLAM PHARMACEUTICALS, INC.
Form 10-Q
November 06, 2014
Table of Contents

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-Q

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

For the quarterly period ended September 30, 2014

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

(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 x No ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted 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 and post such files). Yes x No ¨

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

Large accelerated filer x	Accelerated filer ¨
Non-accelerated filer ¨ (do not check if a smaller reporting company)	Smaller reporting company ¨

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

At October 31, 2014, the registrant had 76,931,090 shares of Common Stock, $0.01 par value per share, outstanding.

Table of Contents

INDEX

	PAGE NUMBER
PART I. FINANCIAL INFORMATION	
ITEM 1. FINANCIAL STATEMENTS (Unaudited)	
CONDENSED CONSOLIDATED BALANCE SHEETS AS OF SEPTEMBER 30, 2014 AND DECEMBER 31, 2013	2
CONDENSED CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS FOR THE THREE AND NINE MONTHS ENDED SEPTEMBER 30, 2014 AND 2013	3
CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS FOR THE NINE MONTHS ENDED SEPTEMBER 30, 2014 AND 2013	4
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS	5
ITEM 2. MANAGEMENT S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS	15
ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK	29
ITEM 4. CONTROLS AND PROCEDURES	29
PART II. OTHER INFORMATION	
ITEM 1. LEGAL PROCEEDINGS	30
ITEM 1A. RISK FACTORS	31
ITEM 6. EXHIBITS	51
SIGNATURES	52

Table of Contents

ALNYLAM PHARMACEUTICALS, INC.

CONDENSED CONSOLIDATED BALANCE SHEETS

(In thousands, except share and per share amounts)

(Unaudited)

	September 30, 2014	December 31, 2013
ASSETS		
Current assets:		
Cash and cash equivalents	$ 82,721	$ 53,169
Marketable securities	507,927	192,701
Investment in equity securities of Regulus Therapeutics Inc.	41,286	
Billed and unbilled collaboration receivables	384	4,248
Prepaid expenses and other current assets	10,699	3,910
Total current assets	643,017	254,028
Marketable securities	324,534	104,602
Investment in equity securities of Regulus Therapeutics Inc.		45,452
Property and equipment, net	18,806	16,448
Total assets	$ 986,357	$ 420,530
LIABILITIES AND STOCKHOLDERS EQUITY		
Current liabilities:		
Accounts payable	$ 5,201	$ 5,896
Accrued expenses	19,799	14,160
Accrued intraperiod tax allocation	856	
Deferred rent	723	1,112
Deferred revenue	30,270	32,696
Total current liabilities	56,849	53,864
Deferred rent, net of current portion	4,502	2,925
Deferred revenue, net of current portion	20,028	93,394
Other liabilities	500	
Total liabilities	81,879	150,183
Commitments and contingencies (Note 3)		
Stockholders equity:		
Preferred stock, $0.01 par value per share, 5,000,000 shares authorized and no shares issued and outstanding at September 30, 2014 and December 31, 2013		
	767	637

Common stock, $0.01 par value per share, 125,000,000 shares authorized; 76,677,045 shares issued and outstanding at September 30, 2014; 63,741,573 shares issued and outstanding at December 31, 2013		
Additional paid-in capital	1,823,766	846,228
Accumulated other comprehensive income	15,186	19,717
Accumulated deficit	(935,241)	(596,235)
Total stockholders equity	904,478	270,347
Total liabilities and stockholders equity	$ 986,357	$ 420,530

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

Table of Contents

ALNYLAM PHARMACEUTICALS, INC.

CONDENSED CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS

(In thousands, except per share amounts)

(Unaudited)

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2014	2013	2014	2013
Net revenues from collaborators	$ 10,972	$ 8,991	$ 26,542	$ 36,320
Operating expenses:				
Research and development [1]	46,273	34,457	134,703	80,851
In-process research and development			220,766	
General and administrative [1]	9,898	6,768	30,341	18,819
Total operating expenses	56,171	41,225	385,810	99,670
Loss from operations	(45,199)	(32,234)	(359,268)	(63,350)
Other income (expense):				
Interest income	753	290	1,779	784
Other income (expense)	524	(12)	365	(18)
Total other income	1,277	278	2,144	766
Loss before income taxes	(43,922)	(31,956)	(357,124)	(62,584)
(Provision for) benefit from income taxes	(67)	2,270	18,118	5,716
Net loss	$ (43,989)	$ (29,686)	$ (339,006)	$ (56,868)
Net loss per common share - basic and diluted	$ (0.58)	$ (0.48)	$ (4.62)	$ (0.93)
Weighted average common shares used to compute basic and diluted net loss per common share	76,408	62,416	73,375	61,103
Comprehensive loss:				
Net loss	$ (43,989)	$ (29,686)	$ (339,006)	$ (56,868)
Unrealized (loss) gain on marketable securities, net of tax	(6,230)	(962)	(3,964)	11,506

Reclassification adjustment for realized gain on marketable securities included in net loss	(567)		(567)	
Comprehensive loss	$ (50,786)	$ (30,648)	$ (343,537)	$ (45,362)

(1) Non-cash stock-based compensation expenses included in operating expenses are as follows:

Research and development	$ 3,781	$ 6,805	$ 10,019	$ 11,092
General and administrative	2,571	2,040	9,604	4,205

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

Table of Contents

ALNYLAM PHARMACEUTICALS, INC.

CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS

(In thousands)

(Unaudited)

	Nine Months Ended September 30,	
	2014	**2013**
Cash flows from operating activities:		
Net loss	$ (339,006)	$ (56,868)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	8,585	7,602
Non-cash stock-based compensation	19,623	15,297
Charge for 401(k) company stock match	513	351
Realized gain on sale of marketable securities	(567)	
Benefit from intraperiod tax allocation	(18,118)	(5,716)
In-process research and development	220,766	
Changes in operating assets and liabilities:		
Proceeds from landlord tenant improvements		192
Billed and unbilled collaboration receivables	3,864	(505)
Prepaid expenses and other assets	(6,789)	(2,222)
Accounts payable	(826)	(1,336)
Accrued expenses and other	7,291	3,871
Deferred revenue	(24,342)	(6,954)
Net cash used in operating activities	(129,006)	(46,288)
Cash flows from investing activities:		
Purchases of property and equipment	(5,435)	(3,128)
Purchases of marketable securities	(852,673)	(335,197)
Sales and maturities of marketable securities	312,859	151,772
Payment for asset acquisition	(25,000)	
Net cash used in investing activities	(570,249)	(186,553)
Cash flows from financing activities:		
Proceeds from exercise of stock options and other types of equity	21,735	19,819
Proceeds from issuance of common stock, net of offering costs		173,572
Proceeds from issuance of common stock to Genzyme	723,037	
Payments for repurchase of common stock for employee tax withholding	(15,965)	(115)
Net cash provided by financing activities	728,807	193,276

Net increase (decrease) in cash and cash equivalents	29,552	(39,565)
Cash and cash equivalents, beginning of period	53,169	51,405
Cash and cash equivalents, end of period	$ 82,721	$ 11,840

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

Table of Contents

ALNYLAM PHARMACEUTICALS, INC.

NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS

(Unaudited)

1. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

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, 2013, which were included in our Annual Report on Form 10-K that was filed with the Securities and Exchange Commission, or SEC, on February 20, 2014. 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 significant intercompany accounts and transactions have been eliminated.

Use of Estimates

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the condensed consolidated financial statements and the reported amounts of revenues and expenses during the reporting period. Actual results could differ from those estimates.

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 (using the treasury stock method) and unvested restricted stock awards. 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 each period 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 September 30,

	2014	2013
Options to purchase common stock	8,082	8,021
Unvested restricted common stock	31	593
	8,113	8,614

Public Offering

In January 2013, we sold an aggregate of 9,200,000 shares of our common stock through an underwritten public offering at a price to the public of $20.13 per share. As a result of this offering, we received aggregate net proceeds of $173.6 million, after deducting underwriting discounts and commissions and other offering expenses of $11.6 million.

Table of Contents

Fair Value Measurements

The fair value is the price that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. The following tables present information about our assets that are measured at fair value on a recurring basis at September 30, 2014 and December 31, 2013, and indicate the fair value hierarchy of the valuation techniques we utilized to determine such fair value. In general, fair values determined by Level 1 inputs utilize quoted prices (unadjusted) in active markets for identical assets or liabilities. Fair values determined by Level 2 inputs utilize data points that are observable, such as quoted prices (adjusted), interest rates and yield curves. Fair values determined by Level 3 inputs utilize unobservable data points for the asset or liability, and include situations where there is little, if any, market activity for the asset or liability. The fair value hierarchy level is determined by the lowest level of significant input. Financial assets measured at fair value on a recurring basis are summarized as follows, in thousands:

Description	At September 30, 2014	Quoted Prices in Active Markets (Level 1)	Significant Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents	$ 68,639	$ 68,639	$	$
Marketable securities (fixed income):				
Corporate notes	658,282		658,282	
U.S. government-sponsored enterprise securities	51,082		51,082	
Municipal debt securities	9,011		9,011	
Commercial paper	107,320		107,320	
Certificates of deposit	6,766		6,766	
Marketable securities (Regulus equity holdings)	41,286	41,286		
Total	$ 942,386	$ 109,925	$ 832,461	$

Description	At December 31, 2013	Quoted Prices in Active Markets (Level 1)	Significant Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents	$ 32,571	$ 32,571	$	$
Marketable securities (fixed income):				
Corporate notes	228,462		228,462	
U.S. government-sponsored enterprise securities	56,863		56,863	
Commercial paper	11,978		11,978	
Marketable securities (Regulus equity holdings)	45,452	45,452		
Total	$ 375,326	$ 78,023	$ 297,303	$

During the nine months ended September 30, 2014, there were no transfers between Level 1 and Level 2 financial assets. The carrying amounts reflected in our condensed consolidated balance sheets for cash, billed and unbilled collaboration receivables, other current assets, accounts payable and accrued expenses approximate fair value due to

their short-term maturities.

Investments in Marketable Securities

We invest our excess cash balances in short-term and long-term marketable debt and equity securities. We classify our investments in marketable debt securities as either held-to-maturity or available-for-sale based on facts and circumstances present at the time we purchased the securities. At each balance sheet date presented, we classified all of our investments in debt and equity securities as available-for-sale. We report available-for-sale investments at fair value at each balance sheet date and include any unrealized holding gains and losses (the adjustment to fair value) in accumulated other comprehensive income (loss), a component of stockholders equity. At September 30, 2014, the balance in our accumulated other comprehensive income was composed solely of activity related to our available-for-sale marketable securities, including our investment in equity securities of Regulus Therapeutics Inc., or Regulus. Realized gains and losses are determined using the specific identification method and are included in other income. We recognized $0.6 million of realized gains from sales of our Regulus available-for-sale securities as other income on our condensed consolidated statements of comprehensive loss during the three and nine month periods ended September 30, 2014. If any adjustment to fair value reflects a decline in the value of the investment, we consider all available evidence to evaluate the extent to which the decline is other than temporary, including our intention to sell and, if so, mark the investment to market through a charge to our condensed consolidated statements of comprehensive loss. We did not record any impairment charges related to our fixed income marketable securities during the current period. Our marketable securities are classified as cash equivalents if the original maturity, from the date of purchase, is 90 days or less, and as marketable securities if the original maturity, from the date of purchase, is in excess of 90 days. Our cash equivalents are composed of money market funds.

Table of Contents

In the fourth quarter of 2012, we began accounting for our investment in Regulus as an available-for-sale marketable security. Intraperiod tax allocation rules require us to allocate our provision for income taxes between continuing operations and other categories of earnings, such as other comprehensive income. In periods in which we have a year-to-date pre-tax loss from continuing operations and pre-tax income in other categories of earnings, such as other comprehensive income, we must allocate the tax provision to the other categories of earnings. We then record a related tax benefit in continuing operations. Upon sales of our available-for-sale marketable securities, we apply the aggregate portfolio approach. As a result, the disproportionate tax effect remains in accumulated other comprehensive income as long as we maintain an investment portfolio.

The following tables summarize the fair value, accumulated other comprehensive income and intraperiod tax allocation regarding our investment in Regulus available-for-sale marketable securities at September 30, 2014 and 2013 and the activity for the three months ended September 30, 2014 and 2013, in thousands:

Description	At June 30, 2014	Sales of Regulus Shares During Three Months Ended September 30, 2014	All Other Activity During Three Months Ended September 30, 2014	Balance at September 30, 2014
Carrying value	$ 12,449	$ (214)	$	$ 12,235
Accumulated other comprehensive income, before tax	37,001	(567)	(7,383)	29,051
Investment in equity securities of Regulus, as reported	$ 49,450	$ (781)	$ (7,383)	$ 41,286
Accumulated other comprehensive income, before tax	$ 37,001	$ (567)	$ (7,383)	$ 29,051
Intraperiod tax allocation recorded as a benefit from income taxes	(14,582)		1,315	(13,267)
Intraperiod tax allocation recorded as an accrued liability	(292)		292	
Accumulated other comprehensive income, net of tax	$ 22,127	$ (567)	$ (5,776)	$ 15,784

Description	At June 30, 2013	Sales of Regulus Shares During Three Months Ended September 30,	All Other Activity During Three Months Ended September 30, 2013	Balance at September 30, 2013

	2013			
Carrying value	$ 12,449	$	$	$ 12,449
Accumulated other comprehensive income, before tax	47,887		(2,337)	45,550
Investment in equity securities of Regulus, as reported	$ 60,336	$	$ (2,337)	$ 57,999
Accumulated other comprehensive income, before tax	$ 47,887	$	$ (2,337)	$ 45,550
Intraperiod tax allocation recorded as a benefit from income taxes	(14,018)		(2,270)	(16,288)
Intraperiod tax allocation recorded as an accrued liability	(5,232)		3,209	(2,023)
Accumulated other comprehensive income, net of tax	$ 28,637	$	$ (1,398)	$ 27,239

Table of Contents

The following tables summarize the fair value, accumulated other comprehensive income and intraperiod tax allocation regarding our investment in Regulus available-for-sale marketable securities at September 30, 2014 and 2013 and the activity for the nine months ended September 30, 2014 and 2013, in thousands:

Description	At December 31, 2013	Sales of Regulus Shares During Nine Months Ended September 30, 2014	All Other Activity During Nine Months Ended September 30, 2014	Balance at September 30, 2014
Carrying value	$ 12,449	$ (214)	$	$ 12,235
Accumulated other comprehensive income, before tax	33,003	(567)	(3,385)	29,051
Investment in equity securities of Regulus, as reported	$ 45,452	$ (781)	$ (3,385)	$ 41,286
Accumulated other comprehensive income, before tax	$ 33,003	$ (567)	$ (3,385)	$ 29,051
Intraperiod tax allocation recorded as a benefit from income taxes	(13,267)			(13,267)
Intraperiod tax allocation recorded as an accrued liability				
Accumulated other comprehensive income, net of tax	$ 19,736	$ (567)	$ (3,385)	$ 15,784

Description	At December 31, 2012	Sales of Regulus Shares During Nine Months Ended September 30, 2013	All Other Activity During Nine Months Ended September 30, 2013	Balance at September 30, 2013
Carrying value	$ 12,449	$	$	$ 12,449
Accumulated other comprehensive income, before tax	26,299		19,251	45,550
Investment in equity securities of Regulus, as reported	$ 38,748	$	$ 19,251	$ 57,999
Accumulated other comprehensive income, before tax	$ 26,299	$	$ 19,251	$ 45,550

Intraperiod tax allocation recorded as a benefit from income taxes	(10,572)		(5,716)	(16,288)
Intraperiod tax allocation recorded as an accrued liability			(2,023)	(2,023)
Accumulated other comprehensive income, net of tax	$ 15,727	$	$ 11,512	$ 27,239

We obtain fair value measurement data for our marketable 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.

The following tables summarize our marketable securities, other than our holdings in Regulus noted above, at September 30, 2014 and December 31, 2013, in thousands:

	At September 30, 2014			
Description	**Amortized Cost**	**Gross Unrealized Gains**	**Gross Unrealized Losses**	**Fair Value**
Corporate notes (Due within 1 year)	$ 378,855	$ 67	$ (84)	$ 378,838
Corporate notes (Due after 1 year through 2 years)	279,967	10	(533)	279,444
U.S. government-sponsored enterprise securities (Due within 1 year)	15,000	3		15,003
U.S. government-sponsored enterprise securities (Due after 1 year through 2 years)	36,155	1	(77)	36,079
Commercial paper (Due within 1 year)	107,314	9	(3)	107,320
Municipal debt securities (Due after 1 year through 2 years)	9,002	9		9,011
Certificates of deposit (Due within 1 year)	6,766			6,766
Total	$ 833,059	$ 99	$ (697)	$ 832,461

	At December 31, 2013			
Description	**Amortized Cost**	**Gross Unrealized Gains**	**Gross Unrealized Losses**	**Fair Value**
Corporate notes (Due within 1 year)	$ 154,175	$ 33	$ (46)	$ 154,162
Corporate notes (Due after 1 year through 2 years)	74,312	23	(35)	74,300
U.S. government-sponsored enterprise securities (Due within 1 year)	26,553	8		26,561
U.S. government-sponsored enterprise securities (Due after 1 year through 2 years)	30,300	2		30,302
Commercial paper (Due within 1 year)	11,983		(5)	11,978
Total	$ 297,323	$ 66	$ (86)	$ 297,303

Table of Contents

Recent Accounting Pronouncements

In May 2014, the Financial Accounting Standards Board, or FASB, issued a new revenue recognition standard which amends revenue recognition principles and provides a single, comprehensive set of criteria for revenue recognition within and across all industries. The new standard provides a five step framework whereby revenue is recognized when promised goods or services are transferred to a customer at an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. The standard also requires enhanced disclosures pertaining to revenue recognition in both interim and annual periods. For public companies, the standard is effective for interim and annual reporting periods beginning after December 15, 2016. Early adoption is not permitted. The standard allows for adoption using a full retrospective method or a modified retrospective method. We are currently evaluating the method of adoption and the expected impact that the standard could have on our condensed consolidated financial statements and related disclosures.

In June 2014, the FASB issued guidance that share-based payment awards with performance targets that affect vesting and could be achieved after the requisite service period should be accounted for as performance conditions. As a result, performance targets are not reflected in estimating the award s grant date fair value. Stock-based compensation expense is recognized over the requisite service period if the achievement of the performance condition is probable. The standard is effective for interim and annual reporting periods beginning after December 15, 2015. Early adoption is permitted. We do not expect the standard will have an impact on our condensed consolidated financial statements and related disclosures since our accounting for share-based payment awards with performance targets is consistent with this guidance.

2. SIGNIFICANT AGREEMENTS

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2014	2013	2014	2013
Takeda	$ 5,494	$ 5,494	$ 16,481	$ 16,481
Monsanto	3,400	1,410	6,220	4,230
Cubist				9,721
Other	2,078	2,087	3,841	5,888
Total net revenues from collaborators	$ 10,972	$ 8,991	$ 26,542	$ 36,320

Product Alliances

Genzyme Collaboration

In January 2014, we entered into a global, strategic collaboration with Genzyme Corporation, a Sanofi company, or Genzyme, to discover, develop and commercialize RNA interference, or RNAi, therapeutics as genetic medicines to treat orphan diseases. The 2014 Genzyme collaboration is governed by a master collaboration agreement, dated January 11, 2014, by and between us and Genzyme, which became effective in February 2014 upon the closing of the equity transaction, described below. The master agreement superseded and replaced the previous collaboration

between us and Genzyme entered into in October 2012 to develop and commercialize RNAi therapeutics targeting transthyretin, or TTR, for the treatment of transthyretin-mediated amyloidosis, or ATTR, including patisiran (ALN-TTR02) and revusiran (the recommended International Nonproprietary Name for ALN-TTRsc).

2012 Genzyme Agreement

In consideration for the rights granted to Genzyme under the 2012 Genzyme agreement, Genzyme paid us an upfront cash payment of $22.5 million. We were also entitled to receive certain milestone payments under the 2012 Genzyme agreement. In the fourth quarter of 2013, we earned a milestone of $7.0 million based upon the completion of a successful patisiran Phase 2 clinical trial and a milestone of $4.0 million based upon the initiation of the Phase 3 clinical trial for patisiran.

Table of Contents

Under the 2012 Genzyme agreement, the parties agreed to collaborate in the development of licensed products, with Genzyme assuming primary responsibility for the development and commercialization of licensed products in the Genzyme territory, which included Japan and the Asia-Pacific region, and us retaining primary responsibility for the development and commercialization of licensed products in the rest of the world. The collaboration between Genzyme and us was governed by a joint steering committee comprised of an equal number of representatives from each party. Genzyme was responsible, at its expense, for all development activities under the development plan reasonably necessary for the regulatory approval and commercialization of an RNAi therapeutic for the treatment of ATTR in the Genzyme territory.

We determined that the deliverables under the 2012 Genzyme agreement included the license, the joint steering committee and any additional TTR-specific RNAi therapeutic compounds that comprised the ALN-TTR program. We also determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the license and undelivered joint steering committee and any additional TTR-specific RNAi therapeutic compounds did not have standalone value due to the specialized nature of the services to be provided by us. In addition, while Genzyme had the ability to grant sublicenses, it could not sublicense all or substantially all of its rights under the 2012 Genzyme agreement. The uniqueness of our services and the limited sublicense right were indicators that standalone value was not present in the arrangement. Therefore the deliverables were not separable and, accordingly, the license and undelivered services were treated as a single unit of account. We were unable to reasonably estimate the period of performance under the 2012 Genzyme agreement, as we were unable to estimate the timeline of our deliverables related to the deliverable for any additional TTR-specific RNAi therapeutic compounds. Through December 31, 2013, we had deferred all revenue, or $33.5 million, under the 2012 Genzyme agreement.

2014 Genzyme Collaboration

In January 2014, we entered into the 2014 Genzyme collaboration. As noted above, the 2014 Genzyme collaboration is governed by a master agreement, which became effective upon the closing of the equity transaction in February 2014 and superseded and replaced the 2012 Genzyme agreement.

The 2014 Genzyme collaboration is structured as an exclusive relationship for the worldwide development and commercialization of RNAi therapeutics in the field of genetic medicines, which includes our current and future genetic medicine programs that reach human proof-of-principal study completion, or Human POP, by the end of 2019, subject to extension to the end of 2021 in various circumstances. We will retain product rights in North America and Western Europe, referred to as the Alnylam Territory, while Genzyme will obtain exclusive rights to develop and commercialize collaboration products in the rest of the world, referred to as the Genzyme Territory, together with certain broader co-development/co-promote or worldwide rights for certain products. Genzyme s rights, described in detail below, are structured as an opt-in that is triggered upon achievement of Human POP. We maintain development control for all programs prior to Genzyme s opt-in and maintain development and commercialization control after Genzyme s opt-in for all programs in the Alnylam Territory.

Specifically, in addition to its regional rights for our current and future genetic medicine programs in the Genzyme Territory, Genzyme will have the right to either (i) co-develop and co-promote ALN-AT3 for the treatment of hemophilia and other rare bleeding disorders in the Alnylam Territory, with us maintaining development and commercialization control, or (ii) obtain a global license to ALN-AS1 for the treatment of hepatic porphyrias. Genzyme will exercise this selection right upon the completion of Human POP for both the ALN-AT3 and ALN-AS1 programs. Finally, Genzyme will have the right for a global license to a single, future genetic medicine program that is not one of our currently defined genetic medicine programs. We will retain global rights to any RNAi therapeutic genetic medicine program that does not reach Human POP by the end of 2019, subject to certain limited exceptions. Under the terms of the master agreement, we retain full rights to all current and future RNAi therapeutic programs

outside of the field of genetic medicines, including the right to form new collaborations.

Under the 2014 Genzyme collaboration, Genzyme s specific license rights include the following:

Regional license terms Upon opt-in, Alnylam will retain product rights in the Alnylam Territory, while Genzyme will obtain exclusive rights to develop and commercialize the product in the Genzyme Territory. Genzyme can elect this license for any of Alnylam s current and future genetic medicine programs that complete Human POP by the end of 2019, subject to limited extension. Development costs for products once Genzyme exercises an option will be shared between Genzyme and us, with Genzyme responsible for twenty percent of the global development costs. Upon the effective date of the 2014 Genzyme collaboration, Genzyme expanded the scope of its regional license and collaboration for patisiran, an RNAi therapeutic currently in a Phase 3 clinical trial for the treatment of ATTR

Table of Contents

patients with familial amyloidotic polyneuropathy, or FAP, which was originally established under the 2012 Genzyme agreement. In consideration for the rights granted to Genzyme under the regional license and collaboration terms for patisiran, Genzyme will be required to make payments totaling up to $50.0 million upon the achievement of certain development milestones. In addition, Genzyme will be required to make payments totaling up to $75.0 million per product other than patisiran, including up to $55.0 million in development milestones and $20.0 million in commercial milestones. Genzyme will also be required to pay tiered double-digit royalties up to twenty percent for each regional product based on annual net sales, if any, of such regional product by Genzyme, its affiliates and sublicensees.

Co-development/co-promote license terms Upon opt-in, Alnylam will retain product rights in the Alnylam Territory, while Genzyme will obtain exclusive rights to develop and commercialize the product in the Genzyme Territory, and will co-promote the product in the Alnylam Territory. Upon the effective date of the 2014 Genzyme collaboration, Genzyme expanded its regional rights for revusiran, an RNAi therapeutic currently in a Phase 2 clinical trial for the treatment of ATTR patients with TTR amyloid cardiomyopathy, which were originally granted under the 2012 Genzyme agreement, to include a co-development/co-promote license and collaboration. Genzyme also has the right to elect a co-development/co-promote license and collaboration for ALN-AT3, if they do not elect a global license and collaboration for ALN-AS1. Development costs for co-development/co-promote products, once Genzyme exercises an option, will be shared between Genzyme and us, with Genzyme responsible for fifty percent of the global development costs. In consideration for the rights granted to Genzyme under the co-development/co-promote license terms, Genzyme will be required to make payments totaling up to $75.0 million in development milestones for each of revusiran and ALN-AT3, if selected. We could potentially earn the next development milestone payment of $25.0 million under the 2014 Genzyme collaboration based upon the initiation of the first global Phase 3 clinical trial for revusiran. Genzyme will also be required to pay tiered double-digit royalties up to twenty percent for each co-development/co-promote product based on annual net sales, if any, in the Genzyme Territory for such co-development/co-promote product by Genzyme, its affiliates and sublicensees. The parties will share profits equally and we will book product sales in the Alnylam Territory.

Global license terms Upon opt-in, Genzyme will obtain a worldwide license to develop and commercialize the product. Genzyme can elect a global license for ALN-AS1, if they do not elect a co-development/co-promote license for ALN-AT3. Genzyme will also have one right to a global license through 2019, subject to limited extension, for a future genetic medicine program that is not one of our currently defined genetic medicine programs. Genzyme shall be responsible for one hundred percent of global development costs. In consideration for the rights granted to Genzyme under the global license terms, Genzyme will be required to make payments totaling up to $200.0 million per product, including up to $60.0 million in development milestones and $140.0 million in commercial milestones. Genzyme will also be required to pay tiered double-digit royalties up to twenty percent for each global product based on annual net sales, if any, of each global product by Genzyme, its affiliates and sublicensees.

Under the master agreement, the parties will collaborate in the development of option products, with us leading development for all programs prior to Genzyme s opt-in and also leading development and commercialization for all programs in the Alnylam Territory after Genzyme s opt-in. If Genzyme does not exercise its option to license rights to a particular program, we will retain the exclusive right to develop and commercialize such program throughout the

world, including the right to sublicense to third parties.

The 2014 Genzyme collaboration is governed by an alliance joint steering committee that is comprised of an equal number of representatives from each party. There will also be additional committees to manage various aspects of each regional, co-developed/co-promoted and global program. We and Genzyme intend to enter into supply agreements to provide for supply of collaboration products to Genzyme for clinical studies, and, at Genzyme s request, commercial sales. Genzyme also has certain rights to manufacture collaboration products. Additionally, Genzyme has certain limited opt-out rights, as specified in the master agreement, upon which products revert fully back to us with no further obligations to Genzyme.

In consideration for the rights granted to Genzyme under the master agreement and pursuant to the terms of a stock purchase agreement dated January 11, 2014, upon the closing of the equity transaction in February 2014, we sold to Genzyme 8,766,338 shares of our common stock and Genzyme paid $700.0 million in aggregate cash consideration to us. We recorded this issuance using the price of our common stock on the date the shares were issued to Genzyme. Based on the common stock price of $85.72, the fair value of the shares issued was $751.5 million, which was $51.5 million in excess of the proceeds received from Genzyme for the issuance of our common stock. This $51.5 million is being amortized on a straight line basis over the performance period, which is currently five years as described below. In addition, due to intraperiod tax allocation rules, upon closing of the equity transaction we recorded a benefit from income taxes of $15.2 million due to the Genzyme equity purchase being recorded in additional paid-in capital, net of tax.

Table of Contents

As a condition to the closing of the equity transaction, Genzyme entered into an investor agreement with us. Under the investor agreement, until the earlier of the fifth anniversary of the expiration or earlier termination of the 2014 Genzyme collaboration and the date on which Genzyme and its affiliates cease to beneficially own at least 5% of our outstanding common stock, Genzyme and its affiliates are bound by certain standstill provisions. The standstill provisions include agreements not to acquire more than 30% of our outstanding common stock, call stockholder meetings, nominate directors other than those approved by our board of directors, subject to certain limited exceptions, or propose or support a proposal to acquire us.

Further, Genzyme has agreed to vote, and cause its affiliates to vote, all shares of our voting securities they are entitled to vote, up to a maximum of 20% of our outstanding common stock, in a manner either as recommended by our board of directors or proportionally with the votes cast by our other stockholders, except with respect to certain change of control transactions or our liquidation or dissolution. Until Genzyme owns less than 7.5% of our outstanding common stock, subject to Genzyme s limited right to maintain its ownership percentage as described below, if we issue common stock or securities convertible into or exercisable for common stock to a third party that holds at least 30% of our outstanding common stock or, in connection with a collaboration or license transaction, to a third party that will initially hold at least the percentage of our outstanding common stock represented by the shares purchased by Genzyme at the closing of the equity transaction, we will offer Genzyme an opportunity to amend the standstill and voting provisions in the investor agreement to be consistent with the terms provided to such third party.

In accordance with the investor agreement, as a result of our issuance of shares in connection with our acquisition of Sirna Therapeutics, Inc., or Sirna, described below, in March 2014, Genzyme exercised its right to purchase an additional 344,448 shares of our common stock for $23.0 million, allowing Genzyme to maintain its ownership level of our common stock of approximately 12%.

We determined that the deliverables for the programs Genzyme is currently collaborating with us on include the licenses to our patisiran and revusiran clinical programs, which licenses were delivered to Genzyme upon the closing date of the transaction, and the associated development activities, joint steering committee participation and information exchange for these clinical programs. We also determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the license and associated undelivered development activities, joint steering committee participation and information exchange activities did not have standalone value due to the specialized nature of the services to be provided by us. In addition, while Genzyme has the ability to grant sublicenses, it cannot sublicense all or substantially all of its rights under the 2014 Genzyme collaboration. The uniqueness of our services and the limited sublicense rights are indicators that standalone value is not present in the arrangement. Therefore the deliverables are not separable and, accordingly, the license and undelivered services were treated as a single unit of account. When multiple deliverables are accounted for as a single unit of account, we base our revenue recognition model on the final deliverable. Under the 2014 Genzyme collaboration, the last deliverables for patisiran and revusiran are expected to be completed within five years.

We determined that the total cash received from Genzyme under the now superseded 2012 Genzyme agreement reflects consideration for certain of the performance obligations for ALN-TTR programs included in the 2014 Genzyme collaboration. Therefore we are recognizing the $33.5 million of deferred revenue under the 2012 Genzyme agreement on a straight-line basis over the period of performance of the ALN-TTR programs, which is currently five years. As future consideration, including any milestones or reimbursement for research and development services, is achieved, we will recognize as revenue a portion of these payments equal to the percentage of the performance period completed when the milestone or service has been satisfied, multiplied by the amount of the payment. We will recognize the remaining portion of consideration received over the remaining performance period on a straight-line basis.

We determined that the opt-in rights that Genzyme has for future genetic medicine programs represent separate and additional deliverables that Genzyme may receive from us in future periods. Upon each opt-in by Genzyme, we have determined that each program and the related activities will represent a single unit of account and, consistent with our accounting policies, we will base our revenue recognition period on the final deliverable associated with each future opt-in, if any.

Table of Contents

Platform Alliance

Monsanto Alliance

In August 2012, we and Monsanto Company, or Monsanto, entered into a license and collaboration agreement pursuant to which we granted to Monsanto a worldwide, exclusive, royalty bearing right and license, including the right to grant sublicenses, to our RNAi platform technology and intellectual property controlled by us as of the date of the Monsanto agreement or during the 30 months thereafter, in the field of agriculture.

In September 2014, we and Monsanto mutually determined not to pursue the discovery collaboration originally contemplated under the terms of the Monsanto agreement. Accordingly, Monsanto will not be required to pay us the final milestone of $1.0 million under the Monsanto agreement. There are no remaining milestones under the Monsanto agreement.

Under the Monsanto agreement, the last deliverable expected to be completed was the discovery collaboration, which was originally to be completed within five years. Therefore, prior to the September 2014 amendment, we were recognizing revenue under the Monsanto agreement on a straight-line basis over five years. However, as a result of the September 2014 amendment, we have determined that the final deliverable in the collaboration is the technology transfer activities, know-how exchange and access to intellectual property controlled by us as of the date of the Monsanto agreement or during the 30 months thereafter, in the field of agriculture. Consequently, we are now recognizing the remaining deferred revenue of $16.8 million at the date of the amendment on a prospective basis from September 2014 through February 2015, the date which is the end of the 30 month obligation, which excludes $5.0 million related to a potential refund due to Monsanto under certain circumstances pursuant to the original terms of the Monsanto agreement. We will continue to recognize this revenue on a straight-line basis over the remaining obligation period. We cannot use a proportional performance model since we are unable to reasonably estimate the level of effort to fulfill these obligations, primarily because the potential effort required is unknown. At September 30, 2014, deferred revenue under the Monsanto agreement was $19.4 million, of which $14.4 million will be recognized through February 2015 and $5.0 million will be recognized when the potential refund obligation ceases and can be considered fixed or determinable.

Asset acquisition

In-process research and development

In January 2014, we entered into a stock purchase agreement with Sirna, Merck Sharp & Dohme Corp., or Merck, and, for limited purposes, Merck & Co., Inc., pursuant to which we purchased from Merck all of Merck s right, title and interest in and to all of the outstanding shares of common stock of Sirna. The Merck transaction closed on March 5, 2014. Sirna possesses intellectual property and RNAi assets including early-stage pre-clinical therapeutic candidates, chemistry, and siRNA-conjugate and other delivery technologies that we intend to integrate into our platform for delivery of RNAi therapeutics.

At the closing of the transaction, we paid Merck $25.0 million in cash and issued 2,142,037 shares of our common stock. We recorded this issuance using the price of our common stock on March 5, 2014, the date that these shares were issued to Merck. Based on the common stock price of $81.36, the fair value of the shares issued was $174.3 million. As a result of the cash payment and issuance of shares to Merck, we recorded a total of $199.3 million to in-process research and development expense. We issued an additional 378,007 shares of common stock to Merck on May 19, 2014 upon the completion of certain technology transfer activities during the second quarter of 2014. In the first quarter of 2014, we recorded a liability of $25.4 million associated with the then future obligation to issue

these shares, based on the then current price of our common stock, which was also charged to in-process research and development expense. Upon completion of these technology transfer activities in the second quarter of 2014, we re-measured the expense recorded in connection with these shares using the then current price of our common stock, resulting in a credit of $3.9 million. We recorded an expense of $220.8 million to in-process research and development for the nine months ended September 30, 2014 as a result of this asset acquisition. In future periods, there will be no additional charges recorded to in-process research and development related to the purchase of the Sirna RNAi assets from Merck.

We accounted for this transaction as an acquisition of in-process research and development assets and recorded the entire amount to in-process research and development expense as we did not acquire any employees, manufacturing or other facilities, developed processes or clinical-stage assets as part of our acquisition of Sirna.

Pursuant to the Sirna agreement, Merck is also eligible to receive the following consideration from us: (i) up to an aggregate of $10.0 million upon the achievement by us or our related parties of specified regulatory milestones for RNAi products covered by Sirna intellectual property, and (ii) up to an aggregate of $105.0 million upon the achievement by us or our related parties of specified development and regulatory ($40.0 million) and commercial ($65.0 million) milestones associated with the clinical development progress of certain pre-clinical candidates discovered by Sirna, together with low single-digit royalties for our products and single-digit royalties for Sirna products, in each case based on annual worldwide net sales, if any, by us and our related parties of any such products.

Table of Contents

Under the Sirna agreement, Merck also agreed not to dispose of (i) any shares of our common stock beneficially owned for a period of six months following the closing date, subject to certain limited exceptions, and (ii) 50% of the shares of our common stock beneficially owned for a period of six additional months following the termination of the initial lock-up, referred to as the Subsequent Lock-Up. During and following the expiration of the Subsequent Lock-Up, Merck will be permitted to sell such shares of our common stock subject to certain limitations, including certain volume and manner of sale restrictions.

3. COMMITMENTS AND CONTINGENCIES

Operating Lease

We lease office and laboratory space located at 300 Third Street, Cambridge, Massachusetts for our corporate headquarters under a non-cancelable real property lease agreement by and between us and ARE-MA Region No. 28, LLC, or the Landlord, dated as of September 26, 2003, as amended by a First Amendment to Lease dated March 16, 2006, a Second Amendment to Lease dated June 26, 2009, a Third Amendment to Lease dated May 11, 2010 and a Fourth Amendment to Lease dated November 4, 2011, referred to collectively as the Lease. Pursuant to the Lease, we lease a total of approximately 129,000 square feet of office and laboratory space. The term of the Lease was set to expire in September 2016.

In March 2014, we and the Landlord entered into a Fifth Amendment to Lease, pursuant to which we exercised our option to extend the Lease for an additional five years, through September 30, 2021. Under the Fifth Amendment to Lease, we have the option to extend the Lease, as amended, for one additional five-year term. As a result of the Fifth Amendment to Lease, our operating lease obligations through 2021 increased by $37.8 million.

Litigation

University of Utah Litigation

On March 22, 2011, The University of Utah, or Utah, filed a civil complaint in the United States District Court for the District of Massachusetts against us, Max Planck Gesellschaft Zur Foerderung Der Wissenschaften e.V. and Max Planck Innovation GmbH, together, Max Planck, the Whitehead Institute for Biomedical Research, or Whitehead, the Massachusetts Institute of Technology, or MIT, and the University of Massachusetts, or UMass, claiming a professor at Utah is the sole inventor or, in the alternative, a joint inventor, of the Tuschl patents. Utah is seeking changes to the inventorship of the Tuschl patents, unspecified damages and other relief. On October 31, 2011, we, Max Planck, Whitehead, MIT and UMass filed a motion to dismiss. Also on October 31, 2011, UMass filed a motion to dismiss on separate grounds, which we, Max Planck, Whitehead and MIT have joined. On December 31, 2011, Utah filed a second amended complaint dropping UMass as a defendant and adding as defendants several UMass officials. In June 2012, the Court denied both motions to dismiss. We, Max Planck, Whitehead, MIT and UMass filed an appeal of the Court s ruling on the motion to dismiss for lack of jurisdiction and a motion requesting that the Court stay the case pending the outcome of the appeal. In July 2012, the Court stayed discovery in the case pending the outcome of the defendants appeal. In August 2013, the United States Court of Appeals for the Federal Circuit, or CAFC, affirmed the lower Court s ruling, in a split decision. In September 2013, we filed a petition with the CAFC for rehearing or rehearing en banc. In November 2013, the CAFC denied our petition for rehearing or rehearing en banc and remanded the case back to the lower Court. In February 2014, we filed a petition for writ of certiorari from the Supreme Court and a motion to stay the lower Court proceedings pending a decision from the Supreme Court on our petition. The lower Court granted our motion to stay the proceedings, however, in June 2014 the Supreme Court denied our petition for certiorari and remanded the case back to the United States District Court for the District of Massachusetts for trial, which is now scheduled to begin on November 2, 2015.

Although we believe we have meritorious defenses and intend to vigorously defend ourselves in this matter, litigation is subject to inherent uncertainty and a court could ultimately rule against us. In addition, the defense of 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. We have not recorded an estimate of the possible loss associated with this legal proceeding due to the uncertainties related to both the likelihood and the amount of any possible loss or range of loss.

Our accounting policy for accrual of legal costs is to recognize such expenses as incurred.

Table of Contents

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. Without limiting the foregoing, the words may, will, should, could, expects, plans, intends, anticipates, believes, estimates, predicts, potential, continue, target, goal 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 biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. RNAi is a naturally occurring biological pathway within cells for selectively silencing and regulating the expression of specific genes. Since many diseases are caused by the inappropriate activity of specific genes, the ability to silence genes selectively through RNAi could provide a new way to treat a wide range of human diseases. We believe that drugs that work through RNAi have the potential to become a broad new class of drugs, like small molecule, protein and antibody drugs. Using our intellectual property and the expertise we have built in RNAi, we are developing a set of biological and chemical methods and know-how that we apply in a systematic way to develop RNAi therapeutics for a variety of diseases.

Our core product strategy, which we refer to as Alnylam 5x15, was launched in January 2011 and is focused on the development and commercialization of novel RNAi therapeutics as genetic medicines. Our genetic medicine programs are RNAi therapeutics directed towards genetically defined targets for the treatment of diseases with high unmet medical need. Under our core product strategy, we expect to have six to seven genetic medicine product candidates in clinical development, including at least two programs in Phase 3 and five to six programs with human proof of concept, by the end of 2015. We are currently advancing the following investigational candidates in clinical or pre-clinical development:

- patisiran (ALN-TTR02), an intravenously delivered RNAi therapeutic targeting transthyretin, or TTR, in development for the treatment of TTR-mediated amyloidosis, or ATTR, in patients with familial amyloidotic polyneuropathy, or FAP;

- revusiran (the recommended International Nonproprietary Name for ALN-TTRsc), a subcutaneously delivered RNAi therapeutic targeting TTR in development for the treatment of ATTR in patients with TTR cardiac amyloidosis, including familial amyloidotic cardiomyopathy, or FAC, and senile systemic

amyloidosis, or SSA;

ALN-AT3, an RNAi therapeutic targeting antithrombin, or AT, in development for the treatment of hemophilia and rare bleeding disorders, or RBD;

ALN-CC5, an RNAi therapeutic targeting complement component C5 in development for the treatment of complement-mediated diseases;

ALN-AS1, an RNAi therapeutic targeting aminolevulinate synthase-1, or ALAS-1, in development for the treatment of hepatic porphyrias, including acute intermittent porphyria, or AIP;

ALN-PCSsc, an RNAi therapeutic targeting proprotein convertase subtilisin/kexin type 9, or PCSK9, in development for the treatment of hypercholesterolemia;

ALN-AAT, an RNAi therapeutic targeting alpha-1-antitrypsin, or AAT, in development for the treatment of AAT deficiency-associated liver disease;

ALN-HBV, an RNAi therapeutic targeting the hepatitis B virus, or HBV, genome, in development for the treatment of HBV infection;

ALN-TMP, an RNAi therapeutic targeting transmembrane protease, serine 6, or TMPRSS6, in development for the treatment of beta-thalassemia and iron-overload disorders;

ALN-ANG, an RNAi therapeutic targeting angioprotein-like 3, or ANGPTL3, in development for the treatment of genetic forms of mixed hyperlipidemia and severe hypertriglyceridemia;

ALN-AC3, an RNAi therapeutic targeting apolipoprotein C-III, or apoCIII, in development for the treatment of hypertriglyceridemia;

ALN-AGT, an RNAi therapeutic targeting angiotensinogen, or AGT, in development for the treatment of hypertensive disorders of pregnancy, including preeclampsia;

ALN-GO1, an RNAi therapeutic targeting glycolate oxidase, or GO, in development for the treatment of primary hyperoxaluria type 1, or PH1; and

other yet to be disclosed programs.

Our strategy is to retain development and commercial rights for our current and future genetic medicine pipeline in North America and Western Europe, while forming alliances with leading, innovative companies for the development and commercialization of these products in the rest of the world. In early 2014, we formed an alliance with Genzyme

Corporation, a Sanofi company, or Genzyme, to develop and commercialize our current Alnylam 5x15 and future genetic medicine pipeline principally in territories outside of North America and Western Europe, subject to certain broader rights. The 2014 Genzyme collaboration is described in more detail below under the heading Strategic Alliances.

Table of Contents

We believe that the strength of our intellectual property portfolio relating to the development and commercialization of small interfering RNAs, or siRNAs, as therapeutics provides us a leading position with respect to this therapeutic modality. Our intellectual property portfolio includes ownership of, or exclusive rights to, issued patents and pending patent applications claiming fundamental features of siRNAs and RNAi therapeutics as well as those claiming crucial chemical modifications and promising delivery technologies. 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. 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.

In addition, our expertise in RNAi therapeutics and broad intellectual property estate have allowed us to form alliances with leading pharmaceutical and life sciences companies, including Isis Pharmaceuticals, Inc., or Isis, Medtronic, Inc., or Medtronic, Novartis Pharma AG, or Novartis, Biogen Idec Inc., or Biogen Idec, F. Hoffmann-La Roche Ltd, or Roche (which assigned its rights and obligations to Arrowhead Research Corporation, or Arrowhead, during 2011), Takeda Pharmaceutical Company Limited, or Takeda, Kyowa Hakko Kirin Co., Ltd., or Kyowa Hakko Kirin, Cubist Pharmaceuticals, Inc., or Cubist, Ascletis BioScience Co., Ltd., or Ascletis, Monsanto Company, or Monsanto, Genzyme and The Medicines Company, or MDCO. We also have established collaborations with and, in some instances, received funding from major medical and disease associations. Finally, to further enable the field and monetize our intellectual property rights, we also grant licenses to biotechnology companies for the development and commercialization of RNAi therapeutics for specified targets in which we have no direct strategic interest under our InterfeRx program, and to research companies that commercialize RNAi reagents or services under our research product licenses.

We also seek to form or advance new ventures and opportunities in areas outside our primary focus on RNAi therapeutics. In 2007, we and Isis established Regulus Therapeutics Inc., or Regulus, a company focused on the discovery, development and commercialization of microRNA therapeutics. In October 2012, Regulus completed its initial public offering and, as of the closing on November 3, 2014 of Regulus recent public offering, we own approximately 12% of Regulus outstanding common stock.

In January 2014, we entered into a stock purchase agreement with Sirna Therapeutics, Inc., or Sirna, Merck Sharp & Dohme Corp., or Merck, and, for limited purposes, Merck & Co., Inc., pursuant to which we purchased from Merck all of Merck s right, title and interest in and to all of the outstanding shares of common stock of Sirna. The Merck transaction closed in March 2014. Sirna possesses intellectual property and RNAi assets including pre-clinical therapeutic candidates, chemistry, and siRNA-conjugate and other delivery technologies that we intend to integrate into our platform for delivery of RNAi therapeutics. We did not acquire any employees, manufacturing or other facilities, developed processes or clinical-stage assets as part of the acquisition of Sirna. In consideration for the Sirna common stock, we (i) paid Merck $25.0 million in cash and (ii) agreed to issue to Merck 2,520,044 shares of our common stock, having a value of $150.0 million as calculated under the terms of the stock purchase agreement on the date of execution. At the closing in March 2014, we issued to Merck 2,142,037 shares of our common stock. We issued the remaining 378,007 shares to Merck in May 2014, upon the completion of certain technology transfer activities during the second quarter of 2014. Merck beneficially owns approximately 3% of our outstanding common stock.

In addition, Merck is eligible to receive the following consideration from us: (i) up to an aggregate of $10.0 million upon the achievement by us or our related parties of specified regulatory milestones for RNAi products covered by Sirna intellectual property, and (ii) up to an aggregate of $105.0 million upon the achievement by us or our related parties of specified development and regulatory ($40.0 million) and commercial ($65.0 million) milestones associated with the clinical development progress of certain pre-clinical candidates discovered by Sirna, together with low single-digit royalties for our products and single-digit royalties for Sirna products, in each case based on annual

worldwide net sales, if any, by us and our related parties of any such products.

We have incurred significant losses since we commenced operations in 2002 and expect such losses to continue for the foreseeable future. At September 30, 2014, we had an accumulated deficit of $935.2 million. Historically, we have generated losses principally from costs associated with research and development activities, acquiring, filing and expanding intellectual property rights and general administrative costs. As a result of planned expenditures for research and development activities relating to our drug development programs, including the development and optimization of drug delivery technologies and clinical trial costs, extension of the capabilities of our technology platform, including through business initiatives, 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 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.

Table of Contents

Although we currently have programs focused on a number of therapeutic areas, we are unable to predict when, if ever, we will successfully develop or be able to commence sales of any product. To date, a substantial portion of our total net revenues has been derived from collaboration revenues from strategic alliances with Roche/Arrowhead, Takeda, Cubist and Novartis, and from the United States government in connection with our development of treatments for hemorrhagic fever viruses, including Ebola. We expect our sources of potential funding for the next several years to be derived primarily from new and existing strategic alliances, which may include license and other fees, funded research and development and milestone payments, and proceeds from the sale of equity or debt.

In January 2013, we sold an aggregate of 9,200,000 shares of our common stock through an underwritten public offering at a price to the public of $20.13 per share. As a result of the offering, we received aggregate net proceeds of $173.6 million, after deducting underwriting discounts and commissions and other offering expenses of $11.6 million.

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. Under our core product strategy, we expect to have six to seven genetic medicine product candidates in clinical development, including at least two programs in Phase 3 and five to six programs with human proof of concept, by the end of 2015. While focusing our efforts on our core product strategy, we also intend to continue to advance additional partner-based development programs through existing or future alliances. In addition, we continue to work internally and with third-party collaborators to develop and optimize new technologies to deliver our RNAi therapeutics both directly to specific sites of disease, and systemically by intravenous or subcutaneous administration.

Our most advanced core product development program, ALN-TTR, targets the TTR gene for the treatment of ATTR. ATTR is an inherited, progressively debilitating and fatal disease caused by a mutation in the TTR gene. We are advancing patisiran as our lead investigational product candidate in our ALN-TTR program. In November 2013, we announced the initiation of our APOLLO Phase 3 clinical trial of patisiran. The APOLLO Phase 3 clinical trial is a randomized, double-blind, placebo-controlled, global study designed to evaluate the efficacy and safety of patisiran in ATTR patients with FAP. We are also conducting a Phase 2 open-label extension, or OLE, study of patisiran for patients treated in our two dose, Phase 2 clinical trial. The Phase 2 OLE study is designed to evaluate the long-term safety and tolerability of patisiran administration. The OLE study is measuring a number of clinical endpoints every six months, including the modified composite Neuropathy Impairment Score, termed mNIS+7. This score is also the primary endpoint of the Phase 3 APOLLO trial of patisiran. Of the 29 patients in the Phase 2 clinical trial, 27 have been enrolled in the Phase 2 OLE study and as of September 30, 2014, 19 patients had received at least six months of treatment with patisiran in the study. The initial results from the ongoing open-label study showed that after six months of treatment, neuropathy impairment scores were essentially unchanged from baseline values. Specifically, there was a mean decrease in mNIS+7 of 0.95 points (N=19), which compares favorably to the increase in mNIS+7 of seven to ten points estimated at six months from historical data sets in untreated FAP patients with similar baseline characteristics. Similar results were observed for the change in Neuropathy Impairment Score, or NIS, where there was a mean increase of 0.22 points at six months (N=20). The stabilization in mNIS+7 was similar in patients with or without concurrent use of TTR tetramer stabilizers. Repeat dosing of patisiran achieved sustained TTR knockdown at the 80% target level for over nine months, and an up to 89.6% level of TTR knockdown was achieved in post-dose measurements. A similar degree of TTR knockdown was observed in patients with or without concurrent use of TTR tetramer stabilizers. There was no significant evidence for disease progression in other clinical assessments, including those from a subgroup of patients with cardiac disease.

Patisiran administration was found to be generally well tolerated in FAP patients (N=27), with minimal adverse events reported for a period of up to one year. As of the time of the data cutoff on September 8, 2014, 282 doses had been

administered with a median of 11 doses per patient. Mean treatment duration was seven months and the longest treatment duration was out to one year. There were no drug-related serious adverse events. Infusion-related reactions were infrequent (14.8%), mild in severity, and did not result in any discontinuations. Two patients experienced serious adverse events regarded as being unrelated to patisiran. Specifically, both patients had fractures with subsequent osteonecrosis, and have continued participation in the study. All other reported adverse events were mild to moderate, and there were no clinically significant changes in liver function tests, renal function tests, or other laboratory or hematological parameters.

In addition to patisiran, we are advancing revusiran, an investigational subcutaneously delivered RNAi therapeutic targeting TTR for the treatment of ATTR in patients with TTR cardiac amyloidosis. We recently announced the completion of enrollment in our Phase 2 clinical trial of revusiran aimed at evaluating the tolerability and preliminary clinical activity of revusiran in patients with FAC and SSA. In this study, revusiran was administered for a total of five weeks, with a total of 26 patients enrolled. Patients completing the Phase 2 trial will be eligible to participate in an OLE study that was recently opened for enrollment. The OLE study will evaluate the safety and tolerability of long-term dosing with revusiran for up to two years, and will also measure effects of treatment toward a number of clinical endpoints, including mortality, hospitalization and six-minute walk distance, in addition to cardiac amyloid burden and function, and cardiac biomarkers.

Table of Contents

We are also evaluating additional cohorts in an ongoing Phase 1 study of revusiran in healthy volunteers to confirm a fixed-dose regimen for further development. In October 2014, we presented updated data from the Phase 1 trial of revusiran conducted in healthy volunteers. Initial results presented in September 2013 showed robust, consistent and statistically significant ($p < 0.01$) knockdown of serum TTR protein levels of up to 94%. The new results included TTR knockdown data for an additional cohort (N=6) receiving doses of 7.5 mg/kg, showing a mean maximum TTR knockdown of 87.9% and a maximum TTR knockdown of 96.2%. Revusiran was generally well tolerated in this study with mild or moderate injection site reactions as the most frequent adverse event, consistent with results from previous cohorts. We plan to initiate a Phase 3 trial for revusiran in patients with TTR cardiac amyloidosis by the end of 2014, and we recently announced that we have completed discussions with the United States Food and Drug Administration, or FDA, and European Medicines Agency, or EMA, regarding the design of this trial.

Under the 2014 Genzyme collaboration, we will lead development and commercialization of patisiran in North America and Western Europe, referred to as the Alnylam Territory, while Genzyme will develop and commercialize the product in the rest of the world, referred to as the Genzyme Territory. In addition, under this collaboration, we and Genzyme have agreed to co-develop and co-commercialize revusiran in the Alnylam Territory, with Genzyme developing and commercializing the product in the Genzyme Territory. This broadened relationship on revusiran is aimed at expanding and accelerating the product s potential global value.

We are also developing ALN-AT3, an investigational RNAi therapeutic targeting AT, a genetically defined target, for the treatment of hemophilia and RBD. ALN-AT3 is a novel therapeutic approach aimed at re-balancing the coagulation cascade and normalizing hemostasis in severe hemophilia A and B patients, including patients with inhibitors against their replacement factor. ALN-AT3 also has potential as a treatment for RBD patients and patients with other bleeding disorders. In January 2014, we initiated a Phase 1 clinical trial with ALN-AT3. The Phase 1 clinical trial is being conducted in the U.K. as a single- and multi-dose, dose-escalation study consisting of two parts. In May 2014, we reported positive top-line results from Part A of the ongoing Phase 1 clinical trial at the World Federation of Hemophilia 2014 World Congress. Part A, which has now been completed, was a randomized, single-blind, placebo-controlled, single-dose, dose-escalation study, intended to enroll up to 24 healthy volunteer subjects. The primary objective of this part of the clinical trial was to evaluate the safety and tolerability of a single dose of ALN-AT3, with the potential secondarily to show changes in AT plasma levels at sub-pharmacologic doses. In Part A of the Phase 1 study, human volunteer subjects received a single subcutaneous dose of ALN-AT3 and, per protocol, the maximum allowable level of AT knockdown was set at 40%. Initial results from the sole dose cohort (n=four, three-to-one, drug-to-placebo) enrolled showed that a single, low subcutaneous ALN-AT3 dose at 0.03 mg/kg resulted in an up to 28-32% knockdown of AT at nadir that was statistically significant relative to placebo ($p < 0.01$ by ANOVA). This resulted in a statistically significant ($p < 0.01$) increase in peak thrombin generation, that was temporally associated and consistent with the degree of AT knockdown. ALN-AT3 was found to be generally well tolerated with no significant adverse events reported. The ongoing multiple ascending dose Part B of the study is designed as an open-label, multi-dose, dose-escalation study enrolling up to 18 people with moderate-to-severe hemophilia A or B. The primary objective of this part of the study is to evaluate the safety and tolerability of multiple doses, specifically three doses, of subcutaneously administered ALN-AT3 in hemophilia subjects. Secondary objectives include assessment of clinical activity as determined by knockdown of circulating AT levels and increase in thrombin generation at pharmacologic doses of ALN-AT3.

The ALN-AT3 Phase 1 human study results are the first to be reported for our Enhanced Stabilization Chemistry, or ESC-GalNAc conjugate technology, which enables subcutaneous dosing with increased potency, durability and a wide therapeutic index. Further, these initial clinical results demonstrate a greater than 50-fold potency improvement with ESC-GalNAc conjugates relative to standard template chemistry conjugates.

In August 2014, we announced that the Committee for Orphan Medicinal Products of the EMA has designated ALN-AT3 as an orphan medicinal product for the treatment of hemophilia A and B. Orphan Drug Designation, or ODD, by the European Commission provides regulatory and financial incentives for companies developing orphan drugs to develop and market therapies that treat a life-threatening or chronically debilitating condition affecting no more than five in 10,000 persons in the EU. In addition to a ten-year period of marketing exclusivity in the EU after product approval, ODD provides companies with protocol assistance from the EMA during the product development phase, direct access to centralized marketing authorization and reduced regulatory fees.

Under the 2014 Genzyme collaboration, Genzyme will have the right to opt-in to the ALN-AT3 program after completion of human proof-of-principal study completion, or Human POP, to *either* co-develop and co-promote ALN-AT3 with us in the Alnylam Territory, with Genzyme developing and commercializing in the Genzyme Territory (subject to its development decision regarding ALN-AS1), *or* to develop and commercialize the product in the Genzyme Territory. In both circumstances, we will lead and control development and commercialization in the Alnylam Territory.

Table of Contents

In November 2014, we announced the approval of our clinical trial application, or CTA, by the U.K. Medicines and Healthcare Products Regulatory Agency to initiate a Phase 1 clinical trial with ALN-PCSsc, an investigational agent for the treatment of hypercholesterolemia. ALN-PCSsc is a subcutaneously administered RNAi therapeutic targeting the gene PCSK9, a target validated by human genetics that is involved in the metabolism of low-density lipoprotein cholesterol, LDL-C or bad cholesterol. The Phase 1 trial of ALN-PCSsc will be conducted in the U.K. as a randomized, single-blind, placebo-controlled, single- and multi-dose, dose-escalation study. The planned Phase 1 trial is designed to enroll up to 76 healthy volunteer subjects with elevated baseline LDL-C (³ 100 mg/dL), with subjects randomized three-to-one, drug-to-placebo. The study will be performed in two phases: a single ascending dose, or SAD, phase and a multiple dose, or MD, phase. In the MD phase, subjects will receive two doses of either ALN-PCSsc or placebo, administered four weeks apart. The MD phase will also include subjects both on and off statin co-medication. The primary objective of the Phase 1 study is to evaluate the safety and tolerability of ALN-PCSsc. Secondary objectives include assessment of clinical activity as determined by knockdown of plasma PCSK9 levels and serum LDL-C levels, as well as pharmacokinetics of ALN-PCSsc. We expect to initiate this Phase 1 study in late 2014 or early 2015. ALN-PCSsc is our third GalNAc-siRNA conjugate to enter a clinical development stage, and the second program using our ESC-GalNAc technology.

In February 2013, we and MDCO entered into a license and collaboration agreement pursuant to which we granted to MDCO an exclusive, worldwide license to develop, manufacture and commercialize RNAi therapeutics targeting PCSK9, including ALN-PCSsc.

We are also advancing several additional programs through pre-clinical development and expect to file two investigational new drug, or IND, applications, or IND equivalents, with respect to these programs in late 2014 or early 2015. These programs include:

- ALN-CC5, an RNAi therapeutic targeting the C5 component of the complement pathway for the treatment of complement-mediated diseases. We expect to file an IND or IND equivalent for ALN-CC5 in late 2014. Under the 2014 Genzyme collaboration, Genzyme will have the right to opt-in to the ALN-CC5 program after completion of Human POP to develop and commercialize the product in the Genzyme Territory. We will lead and control development and commercialization in the Alnylam Territory.

- ALN-AS1, an RNAi therapeutic targeting ALAS-1 for the treatment of AIP. We expect to file an IND or IND equivalent for ALN-AS1 in late 2014 or early 2015. Under the 2014 Genzyme collaboration, Genzyme will have the right to opt-in to the ALN-AS1 program after completion of Human POP to *either* obtain a global license to ALN-AS1 for the treatment of hepatic porphyrias (subject to its development decision regarding ALN-AT3), *or* to develop and commercialize the product in the Genzyme Territory. In the latter case, we will lead and control development and commercialization in the Alnylam Territory.

In addition to the programs described above, we are also advancing other early-stage genetic medicine programs. These programs include: ALN-AAT, an RNAi therapeutic targeting AAT in development for the treatment of AAT deficiency-associated liver disease; ALN-HBV, an RNAi therapeutic targeting the HBV genome in development for the treatment of HBV infection; ALN-TMP, an RNAi therapeutic targeting TMPRSS6 in development for the treatment of beta-thalassemia and iron-overload disorders; ALN-ANG, an RNAi therapeutic targeting ANGPTL3 in development for the treatment of genetic forms of mixed hyperlipidemia and severe hypertriglyceridemia; ALN-AC3, an RNAi therapeutic targeting apoCIII in development for the treatment of hypertriglyceridemia; ALN-AGT, an

RNAi therapeutic targeting AGT in development for the treatment of hypertensive disorders of pregnancy, including preeclampsia; ALN-GO1, an RNAi therapeutic targeting GO in development for the treatment of PH1; and other yet to be disclosed programs. In the case of ALN-AAT, we have selected our development candidate and expect to file an IND or IND equivalent for this program in mid-2015.

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 efficacy of the product candidate. Moreover, there are uncertainties specific to any new field of drug discovery, including RNAi. The successful development of any 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, or the period, if any, in which material net cash inflows will commence from, any potential product candidate. These risks include the uncertainty of:

our ability to discover new product candidates;

our ability to progress product candidates into pre-clinical and clinical trials;

Table of Contents

the scope, rate of progress and cost of our pre-clinical trials and other research and development activities, including those related to developing safe and effective ways of delivering siRNAs into cells and tissues;

the scope, rate of progress and cost of any clinical trials we commence;

clinical trial results;

the cost of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights;

the terms, timing and success of any collaboration, licensing and other arrangements that we may establish;

the cost, timing and success of regulatory filings and approvals or potential changes in regulations that govern our industry or the way in which they are interpreted or enforced;

the cost and timing of establishing sufficient sales, marketing and distribution capabilities;

the cost and timing of establishing sufficient clinical and commercial supplies for any product candidates and products that we may develop;

limits on our ability to research, develop, or manufacture our product candidates as a result of contractual obligations to third parties or intellectual property held by third parties;

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 effect of competing technological and market developments.

Any failure to complete any stage of the development of any potential products in a timely manner 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 development 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

A significant component of our business plan is to enter into strategic alliances and collaborations with leading pharmaceutical and life sciences companies, academic institutions, research foundations and others, as appropriate, to

gain access to funding, capabilities, technical resources and intellectual property to further our development efforts and to generate revenues. We also seek to form or advance new ventures and opportunities in areas outside our primary focus on RNAi therapeutics.

Since delivery of RNAi therapeutics remains an important objective of our research activities, we also look to form collaboration and licensing arrangements with other companies and academic institutions to gain access to delivery technologies. For example, we have entered into agreements with Arrowhead, Tekmira Pharmaceuticals Corporation, or TPC, Protiva Biotherapeutics, Inc., or Protiva, a wholly-owned subsidiary of TPC, and together with TPC, referred to as Tekmira, the Massachusetts Institute of Technology, or MIT, The University of British Columbia, or UBC, and Acuitas Therapeutics Inc. (formerly AlCana Technologies, Inc.), or Acuitas, among others, to focus on various delivery strategies. We have also entered into license agreements with Isis, Max Planck Innovation GmbH (formerly known as Garching Innovation GmbH), or Max Planck Innovation, Tekmira, MIT, Cancer Research Technology Limited, or CRT, and Whitehead Institute for Biomedical Research, or Whitehead, as well as a number of other entities, to obtain rights to intellectual property in the field of RNAi.

To generate revenues from our intellectual property rights, we grant licenses to biotechnology companies under our InterfeRx program for the development and commercialization of RNAi therapeutics for specified targets in which we have no direct strategic interest. We also license key aspects of our intellectual property to companies active in the research products and services market, which includes the manufacture and sale of reagents. We expect our InterfeRx and research product licenses to generate modest near-term revenues that we can re-invest in the development of our proprietary RNAi therapeutics pipeline. At September 30, 2014, we had granted such licenses, on both an exclusive and non-exclusive basis, to approximately 20 companies.

Table of Contents

2014 Genzyme Collaboration. In January 2014, we entered into a global, strategic collaboration with Genzyme to discover, develop and commercialize RNAi therapeutics as genetic medicines to treat orphan diseases. The 2014 Genzyme collaboration is governed by a master collaboration agreement, including the license terms appended thereto, which became effective upon closing of the equity transaction, described below. As of the closing of the equity transaction in February 2014, the master agreement superseded and replaced the 2012 Genzyme agreement, which original Genzyme agreement is described under the heading Strategic Alliances in our annual report on Form 10-K for the year ended December 31, 2012.

The 2014 Genzyme collaboration is structured as an exclusive relationship for the worldwide development and commercialization of RNAi therapeutics in the field of genetic medicines, which includes our current and future genetic medicine programs that reach Human POP by the end of 2019, subject to extension to the end of 2021 in various circumstances. We will retain product rights in the Alnylam Territory, while Genzyme will obtain exclusive rights to develop and commercialize collaboration products in the Genzyme Territory, together with certain broader co-development/co-promote or worldwide rights for certain products. Genzyme s regional, co-development/co-promote and worldwide rights are structured as an opt-in that is triggered upon achievement of Human POP. We will maintain development control for all programs prior to Genzyme s opt-in and maintain development and commercialization control after Genzyme s opt-in for all programs in our territory.

Upon the effective date of the 2014 Genzyme collaboration, Genzyme expanded the scope of its regional license and collaboration for patisiran for the Genzyme Territory. We retain full product rights in the Alnylam Territory. We and Genzyme have also expanded our current collaboration on revusiran, so that we and Genzyme will co-develop and co-promote revusiran in the Alnylam Territory. We will maintain development and commercialization control with revusiran in the Alnylam Territory. Genzyme will develop and commercialize the product in the Genzyme Territory.

In addition to its regional rights for our current and future genetic medicine programs in the Genzyme Territory, Genzyme will have the right to either (i) co-develop and co-promote ALN-AT3 for the treatment of hemophilia and other RBDs in our territory, with us maintaining development and commercialization control, or (ii) obtain a global license to ALN-AS1 for the treatment of hepatic porphyrias. Genzyme will exercise this selection right upon completion of Human POP for both the ALN-AT3 and ALN-AS1 programs. Finally, Genzyme will have the right for a global license to a single, future genetic medicine program that is not one of our currently defined genetic medicine programs. We will retain global rights to any RNAi therapeutic genetic medicine program that does not reach Human POP by the end of 2019, subject to certain limited exceptions. Under the terms of the master agreement, we will retain full rights to all current and future RNAi therapeutic programs outside of the field of genetic medicines, including the right to form new collaborations.

In consideration for the rights granted to Genzyme under the master agreement and pursuant to the terms of a stock purchase agreement, we sold to Genzyme 8,766,338 shares of our common stock and Genzyme paid us $700.0 million in aggregate cash consideration. At the closing, we also entered into an investor agreement with Genzyme. Our investor agreement with Genzyme provides Genzyme with the right, subject to certain exceptions, generally to maintain its ownership position in us until Genzyme owns less than 7.5% of our outstanding common stock, subject to certain additional limited rights of Genzyme to maintain its ownership percentage. In accordance with the investor rights agreement, as a result of our issuance of shares in connection with our acquisition of Sirna in March 2014, on March 25, 2014, Genzyme exercised its right to purchase an additional 344,448 shares of our common stock, at a purchase price of $66.88, the price of our common stock that day, and paid us $23.0 million. This purchase allowed Genzyme to maintain its ownership level of our outstanding common stock of approximately 12%.

A more detailed description of our 2014 Genzyme collaboration and the related stock purchase agreement is set forth in Note 2 to our condensed consolidated financial statements included in Part I, Item 1, Financial Statements, of this

quarterly report on Form 10-Q.

Monsanto Alliance. In August 2012, we and Monsanto entered into a license and collaboration agreement pursuant to which we granted to Monsanto a worldwide, exclusive, royalty bearing right and license, including the right to grant sublicenses, to our RNAi platform technology and intellectual property controlled by us as of the date of the Monsanto agreement or during the 30 months thereafter, in the field of agriculture.

In September 2014, we and Monsanto mutually determined not to pursue the discovery collaboration originally contemplated under the terms of the Monsanto agreement. Accordingly, Monsanto will not be required to pay us the final milestone of $1.0 million under the Monsanto agreement. There are no remaining milestones under the Monsanto agreement.

Table of Contents

microRNA Therapeutics

Regulus. In September 2007, we and Isis established Regulus, a company focused on the discovery, development and commercialization of microRNA therapeutics. Regulus leverages our and Isis technologies, know-how and intellectual property relating to microRNA therapeutics.

Regulus, which initially was established as a limited liability company, converted to a C corporation as of January 2, 2009 and changed its name to Regulus Therapeutics Inc. In consideration for our and Isis initial interests in Regulus, we and Isis each granted Regulus exclusive licenses to our intellectual property for certain microRNA therapeutics as well as certain patents in the microRNA field. Regulus operates as an independent company with a separate board of directors, scientific advisory board and management team, some of whom have options to purchase common stock of Regulus. Members of the board of directors of Regulus who are our employees or Isis employees have not been eligible to receive options to purchase Regulus common stock. In October 2012, Regulus completed an initial public offering. As of the closing on November 3, 2014 of Regulus recent public offering, we own approximately 12% of Regulus outstanding common stock.

Regulus is exploring therapeutic opportunities that arise from microRNA dysregulation. Since microRNAs are believed to regulate broad networks of genes and biological pathways, microRNA therapeutics define a new and potentially high-impact strategy to target multiple nodes on disease pathways. microRNAs are small non-coding RNAs that regulate the expression of other genes. More than 500 microRNAs have been identified to date in humans, each of which is believed to interact with a specific set of genes that control key aspects of cell biology. Since microRNAs may act as master regulators of the genome and are often found to be dysregulated in disease, microRNAs potentially represent an exciting new platform for drug discovery and development. Regulus is advancing microRNA therapeutics in several areas including oncology, fibrosis, hepatitis C virus and metabolic diseases.

Regulus has entered into a number of strategic alliances with leading pharmaceutical companies, including Sanofi, Biogen Idec and AstraZeneca PLC. Each of Alnylam and Isis is entitled to receive specified sublicense income in connection with certain collaborative agreements entered into by Regulus, as well as royalties on net sales, if any, of certain products developed by Regulus or its collaborators, in each case subject to the terms and conditions of the license and collaboration agreement among Regulus, Isis and Alnylam.

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 United States 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 uses; siRNAs directed to specific targets as treatments for particular diseases; delivery technologies, such as in the field of cationic liposomes and conjugates; 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. Our intellectual property portfolio for RNAi therapeutics includes over 1,000 active cases and over 900 granted or issued patents, of which over 400 are issued or granted in the United States, the EU and Japan. We continue to seek to grow our portfolio through the creation of new technology in this field. In addition, we are very active in our evaluation of third-party technologies. To that end, we

recently acquired Sirna s RNAi assets, including an extensive patent estate. The granted patents, applications and know-how obtained through this acquisition further strengthens the breadth and depth of our intellectual property portfolio.

Our expertise in RNAi therapeutics and broad intellectual property portfolio have allowed us to form alliances with leading companies, including Isis, Medtronic, Novartis, Biogen Idec, Roche/Arrowhead, Takeda, Kyowa Hakko Kirin, Cubist, Ascletis, Monsanto, Genzyme and MDCO, as well as enter into license agreements with other biotechnology companies interested in developing RNAi therapeutic products and research companies that commercialize RNAi reagents or services.

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.

Table of Contents

Critical Accounting Policies and Estimates

There have been no significant changes to our critical accounting policies since the beginning of this fiscal year. 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, 2013, which we filed with the SEC on February 20, 2014.

Results of Operations

The following data summarizes the results of our operations for the periods indicated, in thousands:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2014	2013	2014	2013
Net revenues from collaborators	$ 10,972	$ 8,991	$ 26,542	$ 36,320
Operating expenses	56,171	41,225	385,810	99,670
Loss from operations	(45,199)	(32,234)	(359,268)	(63,350)
Net loss	$ (43,989)	$ (29,686)	$ (339,006)	$ (56,868)

The increase in operating expenses for the nine months ended September 30, 2014 resulted from a $220.8 million charge to in-process research and development expense in connection with the purchase of the Sirna RNAi assets from Merck, which is described below under the heading In-process research and development.

Net revenues from collaborators

We generate revenues through research and development collaborations. The following table summarizes our total consolidated net revenues from collaborators, for the periods indicated, in thousands:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2014	2013	2014	2013
Takeda	$ 5,494	$ 5,494	$ 16,481	$ 16,481
Monsanto	3,400	1,410	6,220	4,230
Cubist				9,721
Other	2,078	2,087	3,841	5,888
Total net revenues from collaborators	$ 10,972	$ 8,991	$ 26,542	$ 36,320

Net revenues from collaborators during the three months ended September 30, 2014 were relatively consistent with net revenues from collaborators during the three months ended September 30, 2013. Net revenues from collaborators decreased during the nine months ended September 30, 2014, as compared to the nine months ended September 30, 2013, due primarily to the recognition of the remaining deferred revenue under the Cubist agreement of $9.7 million, due to the termination of the Cubist agreement in February 2013 and the end of our performance obligations thereunder. For the fourth quarter of 2014, we expect net revenues from collaborators to increase as compared to the

amount recorded for the third quarter of 2014 due to an amendment to the Monsanto agreement resulting in the accelerated recognition of the deferred revenue balance at the date of the amendment. Under the amendment to the Monsanto agreement, we will recognize revenue of $8.8 million and $5.6 million, during the three months ending December 31, 2014 and March 31, 2015, respectively, and the remaining $5.0 million of deferred revenues will be recorded upon the cessation of a potential refund obligation under the original Monsanto agreement.

We had $50.3 million of deferred revenue at September 30, 2014, which primarily consists of payments we have received from collaborators, but have not yet recognized pursuant to our revenue recognition policies.

Table of Contents

For the foreseeable future, we expect our revenues to continue to be derived primarily from our alliances with Takeda, Monsanto, MDCO and Genzyme, and other strategic alliances, as well as any new collaborations and licensing activities.

Operating expenses

The following tables summarize our operating expenses for the periods indicated, in thousands and as a percentage of total operating expenses, together with the changes, in thousands and percentages:

	Three Months Ended September 30, 2014	% of Total Operating Expenses	Three Months Ended September 30, 2013	% of Total Operating Expenses	Increase (Decrease) $	Increase (Decrease) %
Research and development	$ 46,273	82%	$ 34,457	84%	$ 11,816	34%
General and administrative	9,898	18%	6,768	16%	3,130	46%
Total operating expenses	$ 56,171	100%	$ 41,225	100%	$ 14,946	36%

	Nine Months Ended September 30, 2014	% of Total Operating Expenses	Nine Months Ended September 30, 2013	% of Total Operating Expenses	Increase (Decrease) $	Increase (Decrease) %
Research and development	$ 134,703	35%	$ 80,851	81%	$ 53,852	67%
In-process research and development	220,766	57%		0%	220,766	N/A
General and administrative	30,341	8%	18,819	19%	11,522	61%
Total operating expenses	$ 385,810	100%	$ 99,670	100%	$ 286,140	287%

Research and development. The following tables summarize the components of our research and development expenses for the periods indicated, in thousands and as a percentage of total research and development expenses, together with the changes, in thousands and percentages:

	Three Months Ended September 30, 2014	% of Expense Category	Three Months Ended September 30, 2013	% of Expense Category	Increase (Decrease) $	Increase (Decrease) %
Research and development						
Clinical trial and manufacturing	$ 17,643	38%	$ 12,198	35%	$ 5,445	45%
Compensation and related	9,722	21%	6,226	18%	3,496	56%
External services	7,510	16%	3,399	10%	4,111	121%
Facilities-related	4,751	11%	3,755	11%	996	27%
Non-cash stock-based compensation	3,781	8%	6,805	20%	(3,024)	(44)%

Lab supplies and materials	1,745	4%	1,154	3%	591	51%
License fees	216	*	222	1%	(6)	(3)%
Other	905	2%	698	2%	207	30%
Total research and development expenses	$ 46,273	100%	$ 34,457	100%	$ 11,816	34%

* Indicates less than 1%

Research and development expenses increased due to additional expenses for clinical trial and manufacturing and external services during the three months ended September 30, 2014 as compared to the three months ended September 30, 2013 due primarily to the significant advancement of certain of our clinical and pre-clinical programs. In addition, compensation and related expenses increased during the three months ended September 30, 2014 as compared to the three months ended September 30, 2013 due primarily to a significant increase in headcount during the period. The decrease in non-cash stock-based compensation expense is due primarily to the granting of stock options that immediately vested upon grant in the third quarter of 2013.

Table of Contents

	Nine Months Ended September 30, 2014	% of Expense Category	Nine Months Ended September 30, 2013	% of Expense Category	Increase (Decrease) $	Increase (Decrease) %
Research and development						
Clinical trial and manufacturing	$ 49,056	36%	$ 21,392	26%	$ 27,664	129%
Compensation and related	27,951	21%	18,227	23%	9,724	53%
External services	18,306	14%	12,390	15%	5,916	48%
Facilities-related	13,415	10%	10,622	13%	2,793	26%
Non-cash stock-based compensation	10,019	7%	11,092	14%	(1,073)	(10)%
License fees	8,799	7%	810	1%	7,989	986%
Lab supplies and materials	4,459	3%	4,025	5%	434	11%
Other	2,698	2%	2,293	3%	405	18%
Total research and development expenses	$ 134,703	100%	$ 80,851	100%	$ 53,852	67%

Research and development expenses increased due to additional expenses for clinical trial and manufacturing and external services during the nine months ended September 30, 2014 as compared to the nine months ended September 30, 2013 due primarily to the significant advancement of certain of our clinical and pre-clinical programs. In addition, compensation and related expense increased during the nine months ended September 30, 2014 as compared to the nine months ended September 30, 2013 due primarily to a significant increase in headcount during the period. License fees increased during the nine months ended September 30, 2014 as compared to the nine months ended September 30, 2013 due to payments to certain entities, primarily fees paid to Isis as a result of the 2014 Genzyme collaboration.

We expect to continue to devote a substantial portion of our resources to research and development expenses as we continue development of our and our collaborators product candidates and focus on continuing to develop drug delivery-related technologies. For the fourth quarter of 2014, we expect that research and development expenses will increase slightly as compared to the third quarter of 2014 based on late-stage clinical development activities.

A significant portion of our research and development expenses are not tracked by project as they benefit multiple projects or our technology platform. Our collaboration agreements may contain cost-sharing arrangements pursuant to which certain costs incurred under the project are reimbursed by the counterparty to such agreement. Costs reimbursed under these agreements could include certain direct external costs and a negotiated full-time equivalent labor rate for the actual time worked on the project. However, while we may track direct external costs attributable to, and the actual time our employees worked on certain of our collaborations agreements, we do not track or manage total research and development expenses by product area or development phase.

In-process research and development. For the nine months ended September 30, 2014, we recorded $220.8 million to in-process research and development expense in connection with the purchase of the Sirna RNAi assets from Merck. Specifically, at the closing of the transaction, we paid Merck $25.0 million in cash and issued 2,142,037 shares of our common stock, resulting in a charge to in-process research and development expense of $199.3 million. We issued an additional 378,007 shares of common stock to Merck in May 2014 upon the completion of certain technology transfer activities during the second quarter of 2014. In the first quarter of 2014, we recorded a liability of $25.4 million associated with the then future obligation to issue these shares, which was also charged to in-process research and development expense. Upon completion of these technology transfer activities in the second quarter of 2014, we re-measured the expense recorded in connection with these shares using the then current price of our common stock,

resulting in a credit of $3.9 million. In future periods, there will be no additional charges recorded to in-process research and development related to the purchase of the Sirna RNAi assets from Merck.

General and administrative. The following tables summarize the components of our general and administrative expenses for the periods indicated, in thousands and as a percentage of total general and administrative expenses, together with the changes, in thousands and percentages:

	Three Months Ended September 30, 2014	% of Expense Category	Three Months Ended September 30, 2013	% of Expense Category	Increase (Decrease) $	Increase (Decrease) %
General and administrative						
Consulting and professional services	$ 3,824	39%	$ 1,854	27%	$ 1,970	106%
Non-cash stock-based compensation	2,571	26%	2,040	30%	531	26%
Compensation and related	2,230	22%	1,769	26%	461	26%
Facilities-related	450	5%	303	5%	147	49%
Other	823	8%	802	12%	21	3%
Total general and administrative expenses	$ 9,898	100%	$ 6,768	100%	$ 3,130	46%

Table of Contents

General and administrative expenses increased during the three months ended September 30, 2014 as compared to the three months ended September 30, 2013 due primarily to an increase in general business activities and certain professional services.

	Nine Months Ended September 30, 2014	% of Expense Category	Nine Months Ended September 30, 2013	% of Expense Category	Increase (Decrease) $	Increase (Decrease) %
General and administrative						
Consulting and professional services	$ 10,756	35%	$ 6,363	34%	$ 4,393	69%
Non-cash stock-based compensation	9,604	32%	4,205	22%	5,399	128%
Compensation and related	6,377	21%	5,146	27%	1,231	24%
Facilities-related	1,526	5%	1,126	6%	400	36%
Other	2,078	7%	1,979	11%	99	5%
Total general and administrative expenses	$ 30,341	100%	$ 18,819	100%	$ 11,522	61%

General and administrative expenses increased during the nine months ended September 30, 2014 as compared to the nine months ended September 30, 2013 due primarily to an increase in non-cash stock-based compensation expenses. This increase was due primarily to a one-time charge recorded for certain stock options that were modified in the second quarter of 2014. In addition, consulting and professional services increased during the nine months ended September 30, 2014 as compared to the nine months ended September 30, 2013 related to business development activities. For the fourth quarter of 2014, we expect that general and administrative expenses will remain consistent as compared to the third quarter of 2014.

Benefit from income taxes

Our benefit from income taxes was $18.1 million for the nine months ended September 30, 2014 as compared to $5.7 million for the nine months ended September 30, 2013. The increase during the nine months ended September 30, 2014 as compared to the nine months ended September 30, 2013 was due to the corresponding income tax benefit associated with the sale of common stock to Genzyme under the 2014 Genzyme collaboration being recorded net of tax to additional paid-in capital.

Liquidity and Capital Resources

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

	Nine Months Ended September 30, 2014	Nine Months Ended September 30, 2013
Net loss	$ (339,006)	$ (56,868)
Adjustments to reconcile net loss to net cash used in operating activities	230,802	17,534

Changes in operating assets and liabilities	(20,802)	(6,954)
Net cash used in operating activities	(129,006)	(46,288)
Net cash used in investing activities	(570,249)	(186,553)
Net cash provided by financing activities	728,807	193,276
Net increase (decrease) in cash and cash equivalents	29,552	(39,565)
Cash and cash equivalents, beginning of period	53,169	51,405
Cash and cash equivalents, end of period	$ 82,721	$ 11,840

Since we commenced operations in 2002, we have generated significant losses. At September 30, 2014, we had an accumulated deficit of $935.2 million. At September 30, 2014, we had cash, cash equivalents and fixed income marketable securities of $915.2 million, compared to cash, cash equivalents and fixed income marketable securities of $350.5 million at December 31, 2013, in each period excluding our investment in equity securities of Regulus.

Table of Contents

In January 2013, we sold an aggregate of 9,200,000 shares of our common stock through an underwritten public offering at a price to the public of $20.13 per share. As a result of this offering, we received aggregate net proceeds of $173.6 million, after deducting underwriting discounts and commissions and other offering expenses of $11.6 million. In February 2014, in consideration for the rights granted to Genzyme under our 2014 Genzyme collaboration, we sold to Genzyme 8,766,338 shares of our common stock and Genzyme paid $700.0 million in aggregate cash consideration to us. In March 2014, as a result of our issuance of shares in connection with our acquisition of Sirna, Genzyme exercised its right under our investor rights agreement to purchase an additional 344,448 shares of our common stock, at a purchase price of $66.88 per share, and paid us $23.0 million.

We invest primarily in cash equivalents, U.S. government-sponsored enterprise securities, municipal obligations, high-grade corporate notes, certificates of deposit and commercial paper. Our investment objectives are, primarily, to assure liquidity and preservation of capital and, secondarily, to obtain investment income. All of our investments in 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 related to our fixed income marketable securities at September 30, 2014.

Operating activities

We have required significant amounts of cash to fund our operating activities as a result of net losses since our inception. For the nine months ended September 30, 2014, net cash used in operating activities of $129.0 million was due primarily to our net loss. For the nine months ended September 30, 2013, net cash used in operating activities of $46.3 million was due primarily to our net loss. In addition, net cash used in operating activities is adjusted for non-cash items to reconcile net loss to net cash used in operating activities. These non-cash adjustments consist primarily of in-process research and development, stock-based compensation, depreciation and amortization.

We expect that we will require significant amounts of cash to fund our operating activities for the foreseeable future as we continue to develop and advance our research and development initiatives. The actual amount of overall expenditures will depend on numerous factors, including the timing of expenses, the timing and terms of collaboration agreements or other strategic transactions, if any, and the timing and progress of our research and development efforts.

Investing activities

For the nine months ended September 30, 2014, net cash used in investing activities of $570.2 million was due primarily to $540.6 million of net purchases of fixed income marketable securities. For the nine months ended September 30, 2013, net cash used in investing activities of $186.6 million was due primarily to $183.4 million of net purchases of fixed income marketable securities.

Financing activities

For the nine months ended September 30, 2014, net cash of $728.8 million provided by financing activities was due primarily to proceeds of $723.0 million received from our issuance of common stock to Genzyme, as well as proceeds of $21.7 million from the issuance of common stock in connection with stock option exercises and other types of equity, partially offset by $16.0 million of payments for the repurchase of common stock for employee tax withholding. For the nine months ended September 30, 2013, net cash provided by financing activities of $193.3 million was due primarily to proceeds of $173.6 million received from our January 2013 underwritten public offering, as well as proceeds of $19.8 million from the issuance of common stock in connection with stock option exercises and other types of equity.

Operating Capital Requirements

We do not know when, if ever, we will successfully develop or be able to commence sales of any product. Therefore, 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 drug development programs, including the development and optimization of drug delivery technologies and clinical trial costs, extension of the capabilities of our technology platform, including through business initiatives, continued management and growth of our patent portfolio, collaborations and general corporate activities. Based on our current operating plan, we believe that our existing cash, cash equivalents and fixed income marketable securities, will be sufficient to fund our planned operations through the launch of our first commercial product. For reasons discussed below, we may require significant additional funds earlier than we currently expect in order to develop, conduct clinical trials for and commercialize any product candidates.

Table of Contents

In the future, we may seek additional funding through additional collaborative arrangements and public or private financings. In December 2012, we filed an automatically effective shelf registration statement with the SEC for an indeterminate number of shares. Additional funding may not be available to us on acceptable terms or at all. In addition, 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 may 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. 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 or product candidates that we would otherwise pursue.

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 progress in demonstrating that siRNAs can be active as drugs;
- our ability to develop relatively standard procedures for selecting and modifying siRNA product candidates;
- progress in our research and development programs, as well as the magnitude of 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, and obtain and maintain licenses to third-party intellectual property;
- 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;

progress in the research and development programs of Regulus; and

the timing, receipt and amount of sales and royalties, if any, from our 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 and Commitments in our Annual Report on Form 10-K for the year ended December 31, 2013. In March 2014, we amended the lease for our Cambridge, Massachusetts facility to exercise our option to extend the lease for an additional five years, through September 30, 2021. As a result, our operating lease obligations through 2021 increased by $37.8 million.

Recent Accounting Pronouncements

In May 2014, the Financial Accounting Standards Board, or FASB, issued a new revenue recognition standard which amends revenue recognition principles and provides a single, comprehensive set of criteria for revenue recognition within and across all industries. The new standard provides a five step framework whereby revenue is recognized when promised goods or services are transferred to a customer at an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. The standard also requires enhanced disclosures pertaining to revenue recognition in both interim and annual periods. For public companies, the standard is effective for interim and annual reporting periods beginning after December 15, 2016. Early adoption is not permitted. The standard allows for adoption using a full retrospective method or a modified retrospective method. We are currently evaluating the method of adoption and the expected impact that the standard could have on our condensed consolidated financial statements and related disclosures.

Table of Contents

In June 2014, the FASB issued guidance that share-based payment awards with performance targets that affect vesting and could be achieved after the requisite service period should be accounted for as performance conditions. As a result, performance targets are not reflected in estimating the award s grant date fair value. Stock-based compensation expense is recognized over the requisite service period if the achievement of the performance condition is probable. The standard is effective for interim and annual reporting periods beginning after December 15, 2015. Early adoption is permitted. We do not expect the standard will have an impact on our condensed consolidated financial statements and related disclosures since our accounting for share-based payment awards with performance targets is consistent with this guidance.

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 and development activities. Our marketable securities consist of U.S. government-sponsored enterprise securities, municipal obligations, high-grade corporate notes, certificates of deposit and commercial paper. 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 September 30, 2014, the net fair value of our interest-sensitive financial instruments would have resulted in a hypothetical decline of $3.3 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. We have not recorded any impairment charges to our fixed income marketable securities at September 30, 2014.

ITEM 4. CONTROLS AND PROCEDURES.

Our management, with the participation of our chief executive officer (principal executive officer) and vice president of finance and treasurer (principal financial officer), evaluated the effectiveness of our disclosure controls and procedures as of September 30, 2014. The term disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or 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 September 30, 2014, our chief executive officer and vice president of finance and treasurer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

No change 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 September 30, 2014 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Table of Contents

PART II. OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS.

University of Utah Litigation

On March 22, 2011, The University of Utah, or Utah, filed a civil complaint in the United States District Court for the District of Massachusetts against us, Max Planck, Whitehead, MIT and University of Massachusetts, or UMass, claiming a professor at Utah is the sole inventor or, in the alternative, a joint inventor, of the Tuschl patents. Utah is seeking changes to the inventorship of the Tuschl patents, unspecified damages and other relief. On October 31, 2011, we, Max Planck, Whitehead, MIT and UMass filed a motion to dismiss. Also on October 31, 2011, UMass filed a motion to dismiss on separate grounds, which we, Max Planck, Whitehead and MIT joined. On December 31, 2011, Utah filed a second amended complaint dropping UMass as a defendant and adding as defendants several UMass officials. In June 2012, the Court denied both motions to dismiss. We, Max Planck, Whitehead, MIT and UMass filed an appeal of the Court s ruling on the motion to dismiss for lack of jurisdiction and a motion requesting that the Court stay the case pending the outcome of the appeal. In July 2012, the Court stayed discovery in the case pending the outcome of the defendants appeal. In August 2013, the United States Court of Appeals for the Federal Circuit, or CAFC affirmed the lower Court s ruling, in a split decision. In September 2013, we filed a petition with the CAFC for rehearing or rehearing en banc. In November 2013, the CAFC denied our petition for rehearing or rehearing en banc and remanded the case back to the lower Court. In February 2014, we filed a petition for writ of certiorari from the Supreme Court and a motion to stay the lower Court proceedings pending a decision from the Supreme Court on our petition. The lower Court granted our motion to stay the proceedings, however, in June 2014 the Supreme Court denied our petition for certiorari and remanded the case back to the United States District Court for the District of Massachusetts for trial, which is now scheduled to begin on November 2, 2015.

Although we believe we have meritorious defenses and intend to vigorously defend ourselves in this matter, litigation is subject to inherent uncertainty and a court could ultimately rule against us. In addition, the defense of 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. We have not recorded an estimate of the possible loss associated with this legal proceeding due to the uncertainties related to both the likelihood and the amount of any possible loss or range of loss.

Table of Contents

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, target, goal and 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 Clinical Stage Company

Because we are in clinical development, there is limited information about our ability to successfully overcome many of the risks and uncertainties encountered by companies in the biopharmaceutical industry.

As a company in clinical development, we have limited experience and have not yet demonstrated an ability to successfully overcome many of the risks and uncertainties frequently encountered by companies in new and rapidly evolving fields, particularly in the biopharmaceutical area. For example, to execute our business plan, we will need to successfully:

- execute product development activities using unproven 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 of our product candidates and market success for any products we commercialize;
- 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 products, raise capital, expand our business or continue our operations.

The approach we are taking to discover and develop novel RNAi therapeutics is unproven and may never lead to marketable products.

We have concentrated our efforts and therapeutic product research on RNAi technology and our future success depends on the successful development of this technology and products based on it. Neither we nor any other company has received regulatory approval to market therapeutics utilizing siRNAs, the class of molecule we are trying to develop into drugs. 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 both preliminary and 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 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 animals or humans. siRNAs may not naturally possess the inherent properties typically required of drugs, such as the ability to be stable in the body long enough to reach the tissues in which their effects are required, nor the ability to enter cells within these tissues in order to exert their effects. We currently have only limited data, and no conclusive evidence, to suggest that we can introduce these drug-like properties into siRNAs. We may spend large amounts of money trying to introduce these properties, and may never succeed in doing so. In addition, these compounds 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. As a result, we may never succeed in developing a marketable product, we may not become profitable and the value of our common stock will decline.

Table of Contents

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 a product candidate 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 September 30, 2014, we had an accumulated deficit of $935.2 million. To date, we have not developed any products nor generated any revenues from the sale of products. Further, we do not expect to generate any product revenues in the foreseeable future. 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. We anticipate that the majority of any revenues we generate over the next several years will be from alliances with pharmaceutical and biotechnology companies, but cannot be certain that we will be able to secure or maintain these 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 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.

We will require substantial additional funds to complete our research and development 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 and market any 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 progress in demonstrating that siRNAs can be active as drugs;

- our ability to develop relatively standard procedures for selecting and modifying siRNA product candidates;

progress in our research and development programs, as well as the magnitude of 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 initiate and complete our pre-clinical and clinical trials, obtain regulatory approvals, and obtain and maintain licenses to third-party intellectual property;

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;

progress in the research and development programs of Regulus; and

the timing, receipt and amount of sales and royalties, if any, from our potential products.

Table of Contents

If our estimates and predictions 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 addition, the terms of any financing may adversely affect the holdings or the rights of our stockholders. For example, if we raise additional funds by issuing equity securities, under our shelf registration statement or otherwise, further dilution to our 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. Moreover, our investor agreement with Genzyme provides Genzyme with the right, subject to certain exceptions, generally to maintain its ownership position in us until Genzyme owns less than 7.5% of our outstanding common stock, subject to certain additional limited rights of Genzyme to maintain its ownership percentage. In accordance with the investor agreement, as a result of our issuance of shares in connection with our acquisition of Sirna in March 2014, Genzyme exercised its right to purchase an additional 344,448 shares of our common stock, and paid us $23.0 million. This purchase allowed Genzyme to maintain its ownership level of approximately 12% of our outstanding common stock. While the exercise of these rights by Genzyme has provided us with an additional $23.0 million in cash, and the exercise in the future by Genzyme may provide us with additional funding under some circumstances, this exercise has caused, and any future exercise of these rights by Genzyme will also cause further, dilution to our stockholders. Debt financing, if available, may involve restrictive covenants that could limit our flexibility in conducting future business activities and, in the event of insolvency, would be paid before holders of equity securities received any distribution of corporate assets.

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 or undergo future reductions in our workforce or other corporate restructuring activities. 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 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. 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.

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

At September 30, 2014, we had $915.2 million in cash, cash equivalents and fixed income marketable securities. We historically have invested these amounts in corporate bonds, 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. 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.

Risks Related to Our Dependence on Third Parties

Our license and collaboration agreements with pharmaceutical companies are important to our business. If these pharmaceutical companies do not successfully develop drugs pursuant to these agreements or we develop drugs targeting the same diseases as our non-exclusive licensees, our business could be adversely affected.

In July 2007, we entered into a license and collaboration agreement with Roche. Under the license and collaboration agreement we granted Roche a non-exclusive license to our intellectual property to develop and commercialize therapeutic products that function through RNAi, subject to our existing contractual obligations to third parties. In November 2010, Roche announced the discontinuation of certain activities in research and early development, including their RNAi research efforts. In October 2011, Arrowhead announced its acquisition of RNA therapeutics assets from Roche, including our license and collaboration agreement with Roche. As a result of the assignment, Arrowhead now has all of the rights and obligations of Roche under that agreement. The license is limited to four therapeutic areas and may be expanded to include additional therapeutic areas, upon payment to us by Arrowhead of

Table of Contents

an additional $50.0 million for each additional therapeutic area, if any. In addition, for each RNAi therapeutic product developed by Arrowhead, its affiliates, or sublicensees under the collaboration agreement, we are entitled to receive milestone payments upon achievement of specified development and sales events, totaling up to an aggregate of $100.0 million per therapeutic target, together with royalty payments based on worldwide annual net sales, if any. Our receipt of milestone payments under this agreement is dependent upon Arrowhead s ability to successfully develop and commercialize RNAi therapeutic products.

In May 2008, we entered into a similar license and collaboration agreement with Takeda, which is limited to two therapeutic areas, and which may be expanded to include additional therapeutic areas, upon payment to us by Takeda of an additional $50.0 million for each additional therapeutic area, if any. For each RNAi therapeutic product developed by Takeda, its affiliates and sublicensees, we are entitled to receive specified development and commercialization milestone payments, totaling up to $171.0 million per product, together with royalty payments based on worldwide annual net sales, if any.

In September 2010, Novartis exercised its right under our collaboration and license agreement to select 31 designated gene targets, for which Novartis has exclusive rights to discover, develop and commercialize RNAi therapeutic products using our intellectual property and technology. Under the terms of the collaboration and license agreement, for any RNAi therapeutic products Novartis develops against these targets, we are entitled to receive milestone payments upon achievement of certain specified development and annual net sales events, up to an aggregate of $75.0 million per therapeutic product, as well as royalties on annual net sales of any such product, if any.

If Takeda, Novartis or Arrowhead fails to successfully develop products using our technology, we may not receive any milestone or royalty payments under our agreements with them. Finally, Takeda or Arrowhead could become a competitor of ours in the development of RNAi-based drugs targeting the same diseases that we choose to target. Takeda has significantly greater financial resources than we do and far more experience in developing and marketing drugs, which could put us at a competitive disadvantage if we were to compete with them in the development of RNAi-based drugs targeting the same disease.

We may not be able to execute our business strategy if we are unable to enter into 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 do not have any capability for sales, marketing or distribution and have limited capabilities for drug development. Accordingly, we have entered into alliances with other companies and collaborators that we believe can provide such capabilities, and we intend to enter into additional such alliances in the future. 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, our goal is to retain development and commercial rights for our current and future genetic medicine pipeline in North America and Western Europe, while forming alliances with leading, innovative companies for the development and commercialization of these products in the rest of the world. In early 2014, we formed an alliance with Genzyme to develop and commercialize our current and future genetic medicine pipeline principally in territories outside of North America and Western Europe, subject to certain broader rights. This broad collaboration replaced our 2012 alliance with Genzyme. With respect to programs that are outside of our core focus on genetic medicines (for example, in the fields of metabolic and infectious disease and in oncology), we intend to seek regional or global alliances. For example, in February 2013, we entered into a global alliance with MDCO to advance our ALN-PCS program.

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) Genzyme for the development and commercialization of patisiran, revusiran and potentially other of our genetic medicine programs in territories outside of North America and Western Europe under the 2014 Genzyme collaboration, and (ii) MDCO for later stage development and commercialization of ALN-PCSsc worldwide. If Genzyme and/or MDCO are not successful in their commercialization efforts, our future revenues from RNAi therapeutics for these indications may be adversely affected.

We may not be successful in entering into such alliances on terms favorable to us due to various factors, including our ability to successfully demonstrate proof of concept for our technology in humans, 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. 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 or sales of an approved drug are lower than we expected. In the case of the Monsanto agreement, if we cease to own or otherwise exclusively control certain licensed patent rights in the agriculture field, resulting in the loss of exclusivity with respect to Monsanto s rights to such patent rights, and such loss of exclusivity has a material adverse effect on the licensed products (as defined in the agreement), we would be required to pay Monsanto up to $5.0 million in liquidated damages, and Monsanto s royalty obligations to us would be reduced or, under certain circumstances, terminated.

Table of Contents

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 that we may develop, we have formed collaborations to fund all or part of the costs of drug development and commercialization, such as our collaboration with MDCO. 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 any other product candidate internally, or to bring any 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 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 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 under certain circumstances. For example, our agreement with MDCO relating to the development and commercialization of ALN-PCS 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 internal sales, distribution and marketing capabilities, 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 and development of RNAi therapeutics, it could delay our development of product candidates, result in the need for additional company resources to develop product candidates, make it more difficult for us to attract new collaborators and could adversely affect how we are perceived in the business and financial communities. For example, in March 2011, Tekmira filed a civil complaint against us claiming, among other things, misappropriation of its confidential and proprietary information and trade secrets. As a result of the litigation, which was settled in November 2012, we were required to expend resources and management attention that would otherwise have been engaged in other activities. In addition, in August 2013, we initiated binding arbitration proceedings to resolve a disagreement with Tekmira regarding the achievement by Tekmira of a $5.0 million milestone payment under our cross-license agreement relating to the manufacture of ALN-VSP clinical trial material for use in China.

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.

Table of Contents

We rely on independent clinical investigators, contract research organizations 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 and data management services. Although we depend heavily on these parties, we do not control them and therefore, we cannot be assured that these third parties will adequately perform all of their contractual obligations to us. 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 may be delayed or terminated.

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

We have very limited manufacturing experience. Some of our product candidates utilize specialized delivery technologies, such as lipid nanoparticle, or LNP-based formulations, whose scale-up and manufacturing could be very difficult. 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. In order to develop products, apply for regulatory approvals and commercialize our products, we will need to develop, contract for, or otherwise arrange for the necessary manufacturing capabilities. Our internal manufacturing capabilities have been 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 for late-stage clinical trial use and early commercial supply.

We may manufacture clinical trial materials ourselves or we may rely on others to manufacture the materials we will require for any clinical trials that we initiate. There are a limited number of manufacturers that supply synthetic siRNAs. We currently rely on several contract manufacturers for our supply of synthetic siRNAs. There are risks inherent in pharmaceutical manufacturing that could affect the ability of our contract manufacturers to meet our delivery time requirements or provide adequate amounts of material to meet our needs. Included in these risks are synthesis and purification failures and contamination during the manufacturing process, which could result in unusable product and cause delays in our development process, as well as additional expense to us. To fulfill our siRNA requirements, we may also need to secure alternative suppliers of synthetic siRNAs 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.

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 legal reasons, we may have access to only one or a limited number of potential manufacturers for such delivery technology. Failure by manufacturers to properly formulate our siRNAs for delivery could result in unusable product. Furthermore, 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 other materials, we have developed cGMP capabilities and processes for the manufacture of patisiran formulated bulk drug product for late-stage clinical use and early commercial supply, and in the future, we may also develop our own capabilities to manufacture drug substance, including siRNAs and siRNA conjugates for human clinical use. In developing these manufacturing capabilities by building our own manufacturing facility, we have incurred substantial expenditures. Also, we have had to, and will likely need to continue to, hire and train qualified employees to staff our new facility. 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 facility in the future, we may also need to secure alternative suppliers of patisiran formulated bulk drug product 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.

The manufacturing process for any 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 manufacturers 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 our commercial collaborators, to produce materials required for commercial supply. We may experience difficulty in obtaining adequate manufacturing capacity for our needs. If we are unable to obtain or maintain contract manufacturing for these 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 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 a third-party manufacturer 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 products that are under development;

Table of Contents

- 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 products could be the subject of inspections by regulatory authorities;
- we may be required to cease distribution or recall some or all batches of our products; and
- ultimately, we may not be able to meet commercial demands for our products.

If any third-party manufacturer with whom we contract 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 third-party manufacturer, which we may not be able to do on reasonable terms, if at all. In some cases, the technical skills required to manufacture our products or product candidates may be unique or proprietary to the original manufacturer 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 manufacturers for any reason, we will be required to verify that the new manufacturer 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 approved by the FDA. The delays associated with the verification of a new manufacturer could negatively affect our ability to develop product candidates in a timely manner or within budget. Furthermore, a manufacturer may possess technology related to the manufacture of our product candidate that such manufacturer owns independently. This would increase our reliance on such manufacturer or require us to obtain a license from such manufacturer in order to have another third party manufacture our products or product candidates.

We have no sales, marketing or distribution experience and would have to invest significant financial and management resources to establish these capabilities.

We have no sales, marketing or distribution experience. We currently expect to rely heavily on third parties to launch and market certain of our product candidates in certain geographies, if approved. However, we intend to commercialize the majority of our genetic medicine programs on our own in North America and Western Europe, and accordingly, we will need to develop internal sales, distribution and marketing capabilities as part of our core product strategy, which will require significant financial and management resources. For our genetic medicine programs where we will perform sales, marketing and distribution functions ourselves, we could face a number of additional risks, including:

- we may not be able to attract and build a significant marketing or sales force;
- the cost of establishing a marketing or sales force may not be justifiable in light of the revenues generated by any particular product; and

our direct sales and marketing efforts may not be successful.

If we are unable to develop our own sales, marketing and distribution capabilities, we will not be able to successfully commercialize our genetic medicine programs without reliance on third parties.

The current credit and financial market conditions may exacerbate certain risks affecting our business.

Due to the 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.

Risks Related to Managing Our Operations

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

We are highly dependent upon our senior management and scientific 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 other business objectives. Our employment agreements with our key personnel are terminable without notice. We do not carry key man life insurance on any of our employees.

Table of Contents

We have grown our workforce over the past year and expect to continue to add a significant number of additional employees during 2015. 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 reward qualified individuals than we do. We may be unable to attract and retain suitably qualified individuals in order to support our growing research and development efforts, and our failure to do so could have an adverse effect on our ability to implement our future business plan.

We may have difficulty expanding our operations successfully as we evolve from a company primarily involved in discovery and pre-clinical testing into one that develops and commercializes drugs.

We expect that as we increase the number of product candidates we are developing we will also need to expand our operations. As noted above, we have grown our workforce over the past year and expect to continue to add a significant number of additional employees during 2015. This expected growth may place a strain on our administrative and operational infrastructure, and we may need to obtain additional space to conduct our operations. If we are unable to 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 expand our development, regulatory, manufacturing, 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 expect that we will need 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.

Our business and operations could suffer in the event of system failures.

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 access, 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 and significantly increase our costs. To the extent that any disruption or security breach were to result in a loss of or damage to our data, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the development of our product candidates could be delayed.

Risks Related to Our Industry

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

Any product candidates we 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 pre-clinical tests and clinical trials to demonstrate the safety and efficacy in humans of our product candidates. Pre-clinical and clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome, and the historical failure rate for product candidates is high. We currently have several programs in clinical development, including patisiran in a Phase 3 clinical trial, revusiran in a

Phase 2 clinical trial and ALN-AT3 in a Phase 1 clinical trial. We have also conducted Phase 1 clinical trials for ALN-PCS02 and ALN-VSP, and Phase 1 and 2 clinical trials for ALN-RSV. However, we may not be able to further advance these or any other product candidate through clinical trials.

If we enter into clinical trials, the results from pre-clinical testing or early clinical trials of a product candidate may not predict the results that will be obtained in subsequent human clinical trials of that product candidate or any other product candidate. For example, patisiran, revusiran and ALN-AT3 each employ novel delivery technologies that have yet to be extensively evaluated in human clinical trials and proven safe and effective. In May 2014, we reported the first human study results for our Enhanced Stabilization Chemistry, or ESC-GalNAc conjugate technology, which enables subcutaneous dosing with increased potency, durability and a wide therapeutic index. While these initial clinical results of ALN-AT3 demonstrated a greater than 50-fold potency improvement with ESC-GalNAc conjugates relative to standard template chemistry conjugates, we cannot assure you that we will see similar results with other clinical candidates.

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 suspend clinical trials of a product candidate at any time for various reasons, including if we or they believe the subjects or patients participating in such trials are being exposed to unacceptable health risks. Among other reasons, adverse side effects of a product candidate on subjects or patients in a clinical trial could result in the FDA or foreign regulatory authorities suspending or terminating the trial and refusing to approve a particular product candidate for any or all indications of use.

Table of Contents

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 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 may experience difficulty enrolling our clinical trials, including, but not limited to, our clinical trials for patisiran, due to the small population of ATTR patients suffering from FAP and the availability of existing approved treatments, as well as other investigational treatments in development. Although our RNAi therapeutics have been generally well tolerated in our clinical trials to date, 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. In addition, in our ALN-VSP and ALN-TTR01 Phase 1 clinical trials, we have reported an incidence of acute infusion reactions occurring in 15-20% of patients. These were graded as mild or moderate in severity and readily responded to slowing of the infusion rate; all patients completed dosing without further incident. The frequency of acute infusion reactions in our ALN-PCS02 and patisiran Phase 1 clinical trials has been less than three percent. In our ALN-PCS02 Phase 1 clinical trial, we reported the occurrence of a mild, transient rash that was observed in sixteen subjects, including four who received placebo; the incidence of this finding was the same in both placebo and drug treatment arms. In our revusiran Phase 1 clinical trial, we observed injection site reactions in a minority of subjects receiving revusiran or placebo. These were reported as being clinically mild and consisted of transient erythema associated in a minority of cases with edema and/or pain. In all cases, these reactions were self-limiting and resolved within approximately two hours of onset. 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 the occurrence of adverse events, can result in increased costs, longer development times or termination of a clinical trial.

Clinical trials also require the review, oversight and approval of IRBs, which continually review clinical investigations and protect the rights and welfare of human subjects. Inability to obtain or delay in obtaining IRB 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 review and approval in support of a marketing application.

Our product candidates that we develop may encounter problems during clinical trials that will cause us, an IRB 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, pre-clinical testing and the clinical trial process that could delay or prevent regulatory approval or our ability to commercialize our product candidates, including:

- our pre-clinical tests or clinical trials may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional pre-clinical testing or clinical trials, or we may abandon projects that we expect to be promising;

delays in filing INDs or comparable foreign applications or delays or failure in obtaining the necessary approvals from regulators or IRBs 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 the FDA or comparable foreign authorities regarding the scope or design of our clinical trials;

problems in engaging IRBs to oversee clinical trials or problems in obtaining or maintaining IRB 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;

Table of Contents

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 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 pre-clinical investigation;

failure of our third-party contractors or investigators to comply with regulatory requirements 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

varying interpretations of data by the FDA and similar foreign regulatory agencies.

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 United States 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, packaging, advertising and promotion, pricing, marketing and distribution of drugs. Rigorous pre-clinical testing and clinical trials and an extensive regulatory approval process are required to be successfully completed in the United States 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 none of the product candidates we may develop will obtain the regulatory approvals necessary for us or our collaborators to begin selling them.

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 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 pre-clinical 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 may 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 clinical development of our product candidates. In addition, because there may be approved treatments for some of the diseases for which we may seek 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. Furthermore, in recent years, there has been increased public and political pressure on the FDA with respect to the approval process for new drugs, and the FDA s standards, especially regarding drug safety, appear to have become more stringent.

Any delay or failure in obtaining required approvals could have a material adverse effect on our ability to generate revenues from the particular product candidate for which we are seeking approval. Furthermore, any regulatory approval to market a product may be subject to limitations on the approved uses for which we may market the product or the labeling or other restrictions. In addition, the FDA has the authority to require a Risk Evaluation and Mitigation Strategy, or REMS, plan as part of a new drug application, or 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. These limitations and restrictions may limit the size of the market for the product and affect reimbursement by third-party payors.

Table of Contents

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 United States and vice versa.

Even if we obtain regulatory approvals, our marketed drugs will be subject to ongoing regulatory review. If we 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 any drugs we may develop, we will also be subject to continuing regulatory review, 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 the drug product required as a condition of approval or agreed to by us. Any regulatory approvals that we receive for our product candidates 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 cGMP requirements and good clinical practices 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 United States, 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.

The manufacturer and manufacturing facilities we use to make any of our product candidates, including our Cambridge facility, will also be subject to periodic review and inspection by the FDA and other regulatory agencies. To date, our manufacturing facility has not been subject to an inspection by any regulatory authority. The discovery of any new or previously unknown problems with us or our third-party manufacturers, or our or their manufacturing processes or facilities, may result in restrictions on the drug or manufacturer or facility, including withdrawal of the drug from the market. We have recently developed cGMP capabilities and processes for the manufacture of patisiran for Phase 3 clinical and early commercial use. We may not have the ability to manufacture material for 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 third-party manufacturers entails risks to which we would not be subject if we manufactured products ourselves, including reliance on the third-party manufacturer for regulatory compliance. We will not have control over our third-party manufacturers compliance with applicable rules and regulations. Our product promotion and advertising will also be subject to regulatory requirements and continuing regulatory review.

If we or our collaborators, manufacturers or service providers fail to comply with applicable continuing regulatory requirements in the United States 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 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;
- relative convenience and ease of administration of our product candidates;
- the willingness of patients to accept potentially new routes of administration;

Table of Contents

the success of our physician education programs;

the availability of adequate government and third-party payor reimbursement;

the pricing of our products, particularly as compared to alternative treatments; and

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 the treatments.

In addition, our estimates regarding the potential market size may be materially different from what we currently expect at the time we commence commercialization, 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.

If we or our collaborators, manufacturers or service providers fail to comply with healthcare laws and regulations, 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 foreign healthcare laws and regulations pertaining to fraud and abuse and patients rights. These laws and regulations include:

the U.S. federal healthcare program anti-kickback law, which prohibits, among other things, persons from soliciting, receiving or providing 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;

the U.S. federal false claims law, which prohibits, 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, and which may apply to us by virtue of statements and representations made to customers or third parties;

the U.S. federal Health Insurance Portability and Accountability Act, or HIPAA, and Health Information Technology for Economic and Clinical Health, or HITECH, Act, which impose requirements relating to the privacy, security, and transmission of individually identifiable health information; and require notification to affected individuals and regulatory authorities of certain breaches of security of individually identifiable health information;

the U.S. federal Open Payments requirements under the National Physician Payment Transparency Program require that manufacturers of pharmaceutical and biological drugs covered by Medicare, Medicaid and Children s Health Insurance Programs report all consulting fees, travel reimbursements, research grants, and other payments or gifts with values over $10 made to physicians and teaching hospitals;

pharmaceutical manufacturers are required to track certain financial arrangements with physicians and teaching hospitals, including any transfer of value made or distributed to such entities, as well as any investment interests held by physicians and their immediate family members. Manufacturers were required by the Patient Protection and Affordable Care Act, or PPACA, to begin tracking this information in 2013 and to report this information to The Centers for Medicare and Medicaid Services, or CMS, which began in 2014; and

state laws comparable to each of the above federal laws, such as, for example, 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 patient data privacy and security.

If our operations are found to be in violation of any such requirements, we may be subject to penalties, including civil or criminal penalties, 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, any of which could adversely affect our financial results. 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.

Table of Contents

If we or our collaborators, manufacturers or service providers fail to comply with applicable federal, state or foreign laws or regulations, we could be subject to enforcement actions, which could affect our ability to develop, market and sell our 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 and fines.

Moreover, federal, state or foreign laws or regulations are subject to change, and while we, our collaborators, manufacturers 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. Although we intend to monitor these regulations, most 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 a number of years. As a result, we might obtain regulatory approval for a product 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.

Our ability to commercialize any 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. Even if we succeed in bringing one or more products to the market, these products may not be considered cost-effective, and the amount reimbursed for any products may be insufficient to allow us to sell our products on a competitive basis. Because most of our programs are in the earlier stages of development, we are unable at this time to determine their cost effectiveness or the likely level or method of reimbursement. Increasingly, the third-party payors who reimburse patients or healthcare providers, such as government and private insurance plans, are requiring that drug companies provide them with predetermined discounts from list prices, and are seeking to reduce the prices charged or the amounts reimbursed for pharmaceutical products. If the price we are able to charge for any products we develop, or the reimbursement provided for such products, is inadequate in light of our development and other costs, our return on investment could be adversely affected.

We currently expect that any drugs we develop may need to be administered under the supervision of a physician on an outpatient basis. 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.

Table of Contents

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. 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. 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 United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement rates. Our inability to promptly obtain coverage and adequate reimbursement rates from both government-funded and private payors for 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. A number of legislative and regulatory changes in the healthcare system in the United States and other major healthcare markets have been proposed in recent years, and such efforts have expanded substantially in recent years. These developments have included prescription drug benefit legislation that was enacted 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 United States in 2010. These developments could, directly or indirectly, affect our ability to sell our products, if approved, at a favorable price.

In particular, in March 2010, the PPACA was signed into law. This new legislation changes the current system of healthcare insurance and benefits intended to broaden coverage and control costs. The new law also contains provisions that will affect companies in the pharmaceutical industry and other healthcare related industries by imposing additional costs and changes to business practices. Provisions affecting pharmaceutical companies include the following:

Mandatory rebates for drugs sold into the Medicaid program have been increased, and the rebate requirement has been extended to drugs used in risk-based Medicaid managed care plans.

The 340B Drug Pricing Program under the Public Health Service Act has been extended to require mandatory discounts for drug products sold to certain critical access hospitals, cancer hospitals and other covered entities.

Pharmaceutical companies are required to offer discounts on brand-name drugs to patients who fall within the Medicare Part D coverage gap, commonly referred to as the Donut Hole.

Pharmaceutical companies are required to pay an annual non-tax deductible fee to the federal government based on each company s market share of prior year total sales of branded products to certain federal

healthcare programs, such as Medicare, Medicaid, Department of Veterans Affairs and Department of Defense. Since we expect our branded pharmaceutical sales to constitute a small portion of the total federal health program pharmaceutical market, we do not expect this annual assessment to have a material impact on our financial condition.

The new 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 full effects of the U.S. healthcare reform legislation cannot be known until the new 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. The new 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 United States.

Moreover, 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 United States to increase pressure on drug pricing. Such reforms could have an adverse effect on anticipated revenues from 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.

Table of Contents

Our ability to obtain services, reimbursement or funding from the federal government may be impacted by possible reductions in federal spending.

Under the Budget Control Act of 2011, the failure of Congress to enact deficit reduction measures of at least $1.2 trillion for the years 2013 through 2021 triggered automatic cuts to most federal programs. These cuts included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, starting in 2013. Under the American Taxpayer Relief Act of 2012, which was enacted on January 1, 2013, the imposition of these automatic cuts was delayed until March 1, 2013. As required by law, President Obama issued a sequestration order on March 1, 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. 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 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 any products we may develop.

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. If we succeed in marketing products, such 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 and may need to obtain higher levels prior to marketing any of our product candidates. 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 involves 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.

Table of Contents

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 United States 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 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 our proposed products or conduct our research and development or other activities. If licenses are not available to us on acceptable terms, we will 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 will 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 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 United States 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 includes a number of changes to the patent laws of the United States. 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 United States 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.

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 will 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, CRT, Isis, MIT, Whitehead, Max Planck Innovation, Tekmira and Arrowhead. 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.

Table of Contents

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 United States 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 manufacture and use as therapeutics, and RNAi-related mechanisms; chemical modifications to siRNAs that improve their suitability for therapeutic uses; siRNAs directed to specific targets as treatments for particular diseases; and delivery technologies, such as in the field of cationic liposomes.

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, reexamination and opposition proceedings, in various patent offices relating to patent rights in the RNAi field. For example, various third parties have initiated oppositions to patents in our Kreutzer-Limmer and Tuschl II series in the European Patent Office, or 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 to apply to our siRNA therapeutic candidates. 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. Thus, it is possible that one or more organizations will hold patent rights to which we will need a license. If those organizations refuse to grant us a license to such patent rights on reasonable terms, we may not be able to market products or perform research and development or other activities covered by these patents.

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. 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. In addition, a third party may claim that we have improperly obtained or used its confidential or proprietary information. For example, in March 2011, Tekmira filed a civil complaint against us alleging, among other things, misappropriation of the plaintiffs confidential and proprietary information and trade secrets. In November 2012, we settled this litigation and

restructured our contractual relationship with Tekmira. In connection with this restructuring, we incurred a $65.0 million charge to operating expenses during the quarter ended December 31, 2012. In addition, during the pendency of the litigation, we incurred significant costs, and the defense of this litigation diverted the attention of our management and other resources that would otherwise have been engaged in other activities.

Furthermore, third parties may challenge the inventorship of our patents or licensed patents. For example, in March 2011, Utah filed a complaint in the United States District Court for the District of Massachusetts against us, Max Planck, Whitehead, MIT and UMass, claiming that a professor of Utah is the sole inventor, or in the alternative, a joint inventor of certain of our in-licensed patents. Utah is seeking correction of inventorship of the Tuschl patents, unspecified damages and other relief. In October 2011, we, Max Planck, Whitehead, MIT and UMass filed a motion to dismiss and UMass filed a motion to dismiss on separate grounds, which we, Max Planck, Whitehead and MIT have joined. In December 2011, Utah filed a second amended complaint dropping UMass as a defendant and adding as defendants several UMass officials. In June 2012, the Court denied both motions to dismiss. We, Max Planck, Whitehead, MIT and UMass filed an appeal of the Court s ruling on the motion to dismiss for lack of jurisdiction and a motion requesting that the Court stay the case pending the outcome of the appeal. In July 2012, the Court stayed discovery in the case

Table of Contents

pending the outcome of the defendants appeal. In August 2013, the United States Court of Appeals for the Federal Circuit, or CAFC, affirmed the lower Court s ruling, in a split decision. In September 2013, we filed a petition with the CAFC for rehearing or rehearing *en banc*. In November 2013, the CAFC denied our petition for rehearing or rehearing en banc and remanded the case back to the lower Court. In February 2014, we filed a petition for writ of certiorari from the Supreme Court and a motion to stay the lower Court proceedings pending a decision from the Supreme Court on our petition. The lower Court granted our motion to stay the proceedings, however, in June 2014 the Supreme Court denied our petition for certiorari and remanded the case back to the United States District Court for the District of Massachusetts for trial, which is now scheduled to begin on November 2, 2015.

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 and development 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 and protecting our RNAi technology and any related 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 and sell products that are covered by the licensed technology or enable a competitor to gain access to the licensed technology. For example, Tekmira has notified us that it believes it has achieved a $5.0 million milestone payment under our cross-license agreement relating to the manufacture of ALN-VSP clinical trial material for use in China. We have notified Tekmira that we do not believe that the milestone has been achieved under the terms of the cross-license agreement. In August 2013, we initiated binding arbitration proceedings seeking a declaratory judgment that Tekmira has not yet met the conditions of the milestone and is not entitled to payment at this time. If it is determined through arbitration that Tekmira has met the requirements of the milestone, we will have to pay Tekmira the milestone.

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 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 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.

Table of Contents

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 pharmaceutical 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. We believe a significant number of drugs are currently under development, and 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 are developing patisiran for the treatment of ATTR patients suffering from FAP. We are aware of other approved products used to treat this disease, as well as product candidates in various stages of clinical development. Patisiran may not compete favorably with these products and product candidates, and even if approved, it may not achieve commercial success.

If we 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;
- 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;

price;

reimbursement coverage; and

patent position.

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. 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.

Table of Contents

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 multiple companies that are working in the field of RNAi. In addition, we granted licenses or options for licenses to Isis, GeneCare Research Institute Co., Ltd., Benitec Ltd., Arrowhead and its subsidiary, Calando Pharmaceuticals, Inc., Tekmira, Quark Pharmaceuticals, Inc., Sylentis S.A.U. and others under which these companies may independently develop RNAi therapeutics against a limited number of targets. Any 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, Arrowhead, as the assignee of Roche, and Takeda have obtained non-exclusive licenses, and Novartis has obtained specific exclusive licenses for 31 gene targets, 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. Isis is currently marketing an antisense drug and has several antisense product candidates in clinical trials, including one for the treatment of ATTR. 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 and may continue to fluctuate significantly in response to factors that are beyond our control. The stock market in general has recently 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 operating performance of these companies. These broad market fluctuations could 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 due to stock volatility.

Our stock price may fluctuate for many reasons, including as a result of public announcements regarding the progress of our development efforts or the development efforts of our collaborators and/or competitors, the addition or departure of our key personnel, variations in our quarterly operating results and changes in market valuations of pharmaceutical and biotechnology companies. When the market price of a stock has been volatile as our stock price may be, holders of that stock have occasionally brought securities class action litigation against the company that issued the stock. If any of our stockholders were to bring a lawsuit of this type against us, even if the lawsuit is without merit, we could incur substantial costs defending the lawsuit. The lawsuit could also divert the time and attention of our management.

Sales of additional shares of our common stock, including by us or our directors and officers, could cause the price of our common stock to decline.

Sales of substantial amounts of our common stock in the public market, or the availability of such shares for sale, by us or our officers and directors, or others, including the issuance of common stock upon exercise of outstanding options or restricted stock, could adversely affect the price of our common stock.

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

Genzyme currently holds approximately 12% of our outstanding common stock and has the right to increase its ownership up to 30%, as well as the right to maintain its ownership percentage through the term of our collaboration, subject to certain limitations. 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.

Table of Contents

Anti-takeover provisions in our charter documents and under Delaware law and our stockholder rights plan 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, our board of directors has adopted a stockholder rights plan, the provisions of which could make it difficult for a potential acquirer of Alnylam to consummate an acquisition transaction. Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner. These provisions would apply even if the proposed merger or acquisition could be considered beneficial by some stockholders.

ITEM 6. EXHIBITS.

10.1	Letter Agreement dated September 5, 2014 by and between the Registrant and Monsanto Company.
12	Computation of Consolidated Ratios of Earnings/Deficiencies to Fixed Charges.
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 September 30, 2014, 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.

Table of Contents

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: November 6, 2014

/s/ John M. Maraganore
John M. Maraganore, Ph.D.
Chief Executive Officer
(Principal Executive Officer)

Date: November 6, 2014

/s/ Michael P. Mason
Michael P. Mason
Vice President of Finance and Treasurer
(Principal Financial and Accounting Officer)