ALNYLAM PHARMACEUTICALS, INC.
Form 10-Q
November 07, 2008

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-Q

þ **QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the quarterly period ended September 30, 2008
OR

o **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 000-50743

ALNYLAM PHARMACEUTICALS, INC.
(Exact name of registrant as specified in its charter)

Delaware	77-0602661
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer 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 þ No o

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 o	Accelerated filer þ	Non-accelerated filer o	Smaller reporting company o

(Do not check if a 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 o No þ

As of October 31, 2008, the registrant had 41,408,489 shares of Common Stock, $0.01 par value per share, outstanding.

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

	September 30, 2008	December 31, 2007
ASSETS		
Current assets:		
Cash and cash equivalents	$ 196,737	$ 105,157
Marketable securities	223,379	350,445
Collaboration receivables	24,140	5,031
Prepaid expenses and other current assets	4,523	2,926
Restricted cash	3,000	
Total current assets	451,779	463,559
Property and equipment, net	19,577	13,810
Marketable securities	100,047	
Intangible assets, net	838	968
Restricted cash, net of current portion	3,152	6,152
Investment in joint venture (Regulus Therapeutics LLC)	4,699	9,129
Other assets	89	173
Total assets	$ 580,181	$ 493,791
LIABILITIES AND STOCKHOLDERS EQUITY		
Current liabilities:		
Accounts payable	$ 3,342	$ 3,826
Accrued expenses	9,859	11,724
Income taxes payable	3,987	3,497
Current portion of notes payable	3,227	3,795
Deferred rent	1,561	1,387
Deferred revenue	80,048	59,249
Total current liabilities	102,024	83,478
Deferred rent, net of current portion	3,122	3,813
Deferred revenue, net of current portion	269,441	204,067
Notes payable, net of current portion	719	2,963
Other long-term liabilities	318	302
Total liabilities	375,624	294,623
Commitments and contingencies		
Stockholders equity:		

Preferred stock, $0.01 par value, 5,000,000 shares authorized and no shares issued and outstanding at September 30, 2008 and December 31, 2007		
Common stock, $0.01 par value, 125,000,000 shares authorized; 41,385,021 and 40,772,967 shares issued and outstanding at September 30, 2008 and December 31, 2007, respectively	414	408
Additional paid-in capital	448,092	424,453
Accumulated other comprehensive (loss) income	(1,099)	300
Accumulated deficit	(242,850)	(225,993)
Total stockholders equity	204,557	199,168
Total liabilities and stockholders equity	$ 580,181	$ 493,791

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

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2008	2007	2008	2007
Net revenues from research collaborators	$ 25,734	$ 16,315	$ 71,759	$ 32,665
Operating expenses:				
Research and development [1]	22,105	59,575	71,940	105,059
General and administrative [1]	6,863	8,078	19,841	17,891
Total operating expenses	28,968	67,653	91,781	122,950
Loss from operations	(3,234)	(51,338)	(20,022)	(90,285)
Other income (expense):				
Equity in loss of joint venture (Regulus Therapeutics LLC)	(2,181)	(139)	(5,415)	(139)
Interest income	3,486	4,311	11,735	9,579
Interest expense	(176)	(272)	(616)	(833)
Other expense	(1,546)	(169)	(1,876)	(265)
Total other income (expense)	(417)	3,731	3,828	8,342
Loss before income taxes	(3,651)	(47,607)	(16,194)	(81,943)
Benefit from (provision for) income taxes	793	(5,185)	(663)	(5,185)
Net loss	$ (2,858)	$ (52,792)	$ (16,857)	$ (87,128)
Net loss per common share basic and diluted	$ (0.07)	$ (1.35)	$ (0.41)	$ (2.29)
Weighted average common shares used to compute basic and diluted net loss per common share	41,197	39,025	40,948	37,984
Comprehensive loss:				
Net loss	$ (2,858)	$ (52,792)	$ (16,857)	$ (87,128)
Foreign currency translation	433	(687)	(56)	(605)
Unrealized gain (loss) on marketable securities	130	273	(1,342)	108
Comprehensive loss	$ (2,295)	$ (53,206)	$ (18,255)	$ (87,625)

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

Research and development	$ 2,908	$ 5,667	$ 8,079	$ 7,687
General and administrative	1,741	2,255	4,938	4,181

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

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

	Nine Months Ended September 30,	
	2008	**2007**
Cash flows from operating activities:		
Net loss	$ (16,857)	$ (87,128)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	3,928	3,180
Deferred income tax provision	16	1,889
Non-cash stock-based compensation	13,903	11,868
Non-cash license expense		7,909
Charge for 401(k) company stock match	292	204
Equity in loss of joint venture (Regulus Therapeutics LLC)	4,530	139
Impairment on equity investment	1,561	
Changes in operating assets and liabilities:		
Proceeds from landlord for tenant improvements	581	295
Collaboration receivables	(19,109)	(1,292)
Prepaid expenses and other assets	(1,597)	(5,546)
Accounts payable	(484)	2,968
Income taxes payable	366	3,296
Accrued expenses and other	(2,963)	7,057
Deferred revenue	86,173	260,118
Net cash provided by operating activities	70,340	204,957
Cash flows from investing activities:		
Purchases of property and equipment	(9,480)	(3,554)
Disposals of property and equipment		2,343
Purchases of marketable securities	(393,292)	(356,264)
Sales and maturities of marketable securities	417,409	177,738
Investment in joint venture (Regulus Therapeutics LLC)	(100)	(10,000)
Net cash provided by (used in) investing activities	14,537	(189,737)
Cash flows from financing activities:		
Proceeds from issuance of common stock	4,043	59,364
Proceeds from issuance of shares to Novartis	5,408	
Proceeds from notes payable		957
Repayments of notes payable	(2,812)	(2,441)
Net cash provided by financing activities	6,639	57,880
Effect of exchange rate on cash	64	(508)
Net increase in cash and cash equivalents	91,580	72,592

Cash and cash equivalents, beginning of period	105,157	127,955
Cash and cash equivalents, end of period	$ 196,737	$ 200,547

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

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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. (the Company or Alnylam) are unaudited and have been prepared in accordance with accounting principles generally accepted in the United States of America applicable to interim periods and, in the opinion of management, include all normal and recurring adjustments that are necessary to present fairly the results of operations for the reported periods. The Company s condensed consolidated financial statements have also been prepared on a basis substantially consistent with, and should be read in conjunction with, the Company s audited consolidated financial statements for the year ended December 31, 2007, which were filed in the Company s Annual Report on Form 10-K with the Securities and Exchange Commission (the SEC) on March 10, 2008. The results of the Company s operations for any interim period are not necessarily indicative of the results of the Company s operations for any other interim period or for a full fiscal year.

The accompanying condensed consolidated financial statements reflect the operations of the Company and its wholly-owned subsidiaries, Alnylam U.S., Inc., Alnylam Europe AG (Alnylam Europe) and Alnylam Securities Corporation. All significant intercompany accounts and transactions have been eliminated. The Company uses the equity method of accounting to account for its investment in Regulus Therapeutics LLC (Regulus Therapeutics).

Use of Estimates

The preparation of financial statements in conformity with accounting principles generally accepted in the United States of America 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 consolidated financial statements and the reported amounts of revenues and expenses during the reporting period. Actual results could differ from those estimates.

Reclassifications

Certain reclassifications have been made to prior years financial statements to conform to the 2008 presentation.

Net Loss Per Common Share

The Company accounts for and discloses net loss per common share in accordance with Statement of Financial Accounting Standards (SFAS) No. 128, *Earnings per Share.* Basic net loss per common share is computed by dividing net loss attributable to common stockholders by the weighted average number of common shares outstanding. Diluted net loss per common share is computed by dividing net loss attributable to common stockholders 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 the periods presented the potential common shares (prior to consideration of the treasury stock method) excluded from the calculation of net loss per common share because their inclusion would be anti-dilutive, in thousands:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2008	2007	2008	2007
Options to purchase common stock	5,716	4,017	5,716	4,017
Unvested restricted common stock	57	57	57	57
Options that were exercised before vesting		8		14
	5,773	4,082	5,773	4,088

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Fair Value Measurements

In September 2006, the Financial Accounting Standards Board (FASB) issued SFAS No. 157, *Fair Value Measurements* (SFAS 157), which addresses how companies should measure fair value when they are required to do so for recognition or disclosure purposes. The standard provides a common definition of fair value and is intended to make the measurement of fair value more consistent and comparable as well as to improve disclosures about those measures. This standard formalizes the measurement principles to be utilized in determining fair value for purposes such as derivative valuation and impairment analysis. In November 2007, the FASB deferred the effective date of SFAS 157 for certain non-financial and non-recurring assets and liabilities. Other than the partial deferral, SFAS 157 became effective for the Company beginning in 2008. The partial adoption of SFAS 157 by the Company has had no impact on the Company s operating results or financial position. The Company is evaluating the impact, if any, full adoption of this standard will have on its non-financial assets and liabilities. For recognition purposes, on a recurring basis, the Company is required to measure certain cash equivalents and available-for-sale investments at fair value. Changes in the fair value of these investments historically have been insignificant.

The following table presents information about the Company s assets that are measured at fair value on a recurring basis as of September 30, 2008, and indicates the fair value hierarchy of the valuation techniques the Company 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, interest rates and yield curves. Fair values determined by Level 3 inputs are unobservable data points for the asset or liability, and include situations where there is little, if any, market activity for the asset or liability. Financial assets and liabilities measured at fair value on a recurring basis are summarized as follows, in thousands:

Description	As of September 30, 2008	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents	$ 194,858	$ 161,799	$ 33,059	$
Marketable securities (fixed income)	322,081		322,081	
Marketable securities (equity holdings)	1,345	1,345		
Total	$ 518,284	$ 163,144	$ 355,140	$

The carrying amounts reflected in the Company s condensed consolidated balance sheets for cash, collaboration receivables, other current assets, accounts payable and accrued expenses approximate fair value due to their short-term maturities.

The Company adopted the provisions of SFAS No. 159, *The Fair Value Option for Financial Assets and Financial Liabilities* (SFAS 159), effective January 1, 2008. SFAS 159 allows an entity the irrevocable option to elect fair value for the initial and subsequent measurement for certain financial assets and liabilities on a contract-by-contract basis. The Company has not elected the fair value option for any of its financial assets or liabilities in the nine months ended September 30, 2008.

Recent Accounting Pronouncements

In December 2007, the FASB reached a consensus on Emerging Issues Task Force (EITF) Issue No. 07-1, *Accounting for Collaborative Arrangements* (EITF 07-1). EITF 07-1 requires collaborators to present the results of activities for which they act as the principal on a gross basis and report any payments received from (made to) other collaborators based on other applicable GAAP or, in the absence of other applicable GAAP, based on analogy to authoritative accounting literature or a reasonable, rational and consistently applied accounting policy election. Further, EITF 07-1 clarifies that the determination of whether transactions within a collaborative arrangement are part of a vendor-customer (or analogous) relationship subject to EITF Issue No. 01-9, *Accounting for Consideration*

Given by a Vendor to a Customer (Including a Reseller of the Vendor s Products). EITF 07-1 will be effective for the Company beginning on January 1, 2009. The Company is evaluating the potential impact of EITF 07-1 on its consolidated financial statements.

In December 2007, the FASB issued SFAS No. 141R, *Business Combinations* (SFAS 141R). SFAS 141R establishes principles and requirements for how an acquirer recognizes and measures in its financial statements the identifiable assets acquired,

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the liabilities assumed, any noncontrolling interest in the acquiree and the goodwill acquired. SFAS 141R also establishes disclosure requirements to enable the evaluation of the nature and financial effects of the business combination. SFAS 141R is effective for fiscal years beginning after December 15, 2008. The Company is evaluating the potential impact of SFAS 141R on its consolidated financial statements.

In December 2007, the FASB issued SFAS No. 160, *Noncontrolling Interests in Consolidated Financial Statements, an amendment of ARB No. 51* (SFAS 160). SFAS 160 changes the accounting for and reporting of noncontrolling or minority interests (now called noncontrolling interests) in consolidated financial statements. SFAS 160 is effective January 1, 2009. When implemented, prior periods will be recast for the changes required by SFAS 160. The Company does not anticipate the adoption of SFAS 160 will have a material impact on its consolidated financial statements.

In May 2008, the FASB issued SFAS No. 162, *The Hierarchy of Generally Accepted Accounting Principles* (SFAS 162). SFAS 162 identifies the sources of accounting principles and the framework for selecting the principles used (order of authority) in the preparation of financial statements that are presented in conformity with generally accepted accounting standards in the United States. SFAS 162 is effective 60 days following the SEC s approval of the Public Company Accounting Oversight Board amendments to AU Section 411, *The Meaning of Present Fairly in Conformity with Generally Accepted Accounting Principles*. The Company does not anticipate the adoption of SFAS 162 will have a material impact on its consolidated financial statements.

2. NOTES PAYABLE

In March 2006, the Company entered into an agreement with Oxford Finance Corporation (Oxford) to establish an equipment line of credit for up to $7.0 million to help support capital expansion of the Company s facility in Cambridge, Massachusetts and capital equipment purchases. The agreement allowed the Company to draw down amounts under the line of credit through December 31, 2007 upon adherence to certain conditions. All borrowings under this line of credit are collateralized by the assets financed and the agreement contains certain provisions that restrict the Company s ability to dispose of or transfer these assets. During 2006 and 2007, the Company borrowed an aggregate of $5.2 million from Oxford pursuant to the agreement at fixed rates ranging from 10.0% to 10.4%, maturing at various times through May 2011. As of September 30, 2008, there was $2.1 million outstanding under this line of credit with Oxford.

In March 2004, the Company entered into an agreement with Lighthouse Capital Partners V, L.P. (Lighthouse) to establish an equipment line of credit for $10.0 million. In June 2005, the parties amended the agreement to allow the Company to draw down amounts under the line of credit through December 31, 2005 upon adherence to certain conditions. All borrowings under the line of credit are collateralized by the assets financed and the agreement contains certain provisions that restrict the Company s ability to dispose of or transfer these assets. The outstanding principal bears interest at fixed rates of 9.25% to 10.25% and matures at various dates through December 2009. On the maturity of each equipment advance under the line of credit, the Company is required to pay, in addition to the principal and interest due, an additional amount of 11.5% of the original principal. This amount is being accrued over the applicable borrowing period as additional interest expense. As of September 30, 2008, there was $1.8 million outstanding under this line of credit with Lighthouse.

At September 30, 2008, future cash payments under the notes payable to Lighthouse and Oxford, including interest, were as follows, in thousands:

Remainder of 2008	$ 1,067
2009	3,513
2010	480
2011	79
Total through 2011	5,139
Less: portion representing interest	1,193
Principal	3,946

Less: current portion	3,227
Long-term notes payable	$ 719

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3. SIGNIFICANT AGREEMENTS

Roche Alliance

In July 2007, the Company and, for limited purposes, Alnylam Europe, entered into a license and collaboration agreement (the LCA) with F. Hoffmann-La Roche Ltd (Roche Basel) and Hoffman-La Roche Inc. (together with Roche Basel, Roche). Under the LCA, which became effective in August 2007, the Company granted Roche a non-exclusive, worldwide, royalty-bearing license to the Company s intellectual property to develop and commercialize therapeutic products that function through RNA interference (RNAi), subject to the Company s existing contractual obligations to third parties. The license is limited to the therapeutic areas of oncology, respiratory diseases, metabolic diseases and certain liver diseases, and the license may be expanded to include other therapeutic areas of up to approximately 20 additional fields upon payment of an additional specified amount for each field.

In consideration for the rights granted to Roche under the LCA, Roche paid the Company $273.5 million in upfront cash payments. Roche is also required to make payments to the Company upon achievement of specified development and sales milestones set forth in the LCA and royalty payments based on worldwide annual net sales, if any, of RNAi therapeutic products by Roche, its affiliates and sublicensees.

Under the LCA, the Company and Roche also agreed to collaborate on the discovery of RNAi therapeutic products directed to one or more disease targets (Discovery Collaboration), subject to the Company s existing contractual obligations to third parties. The Discovery Collaboration between Roche and the Company will be governed by a joint steering committee for a period of five years that is comprised of an equal number of representatives from each party. In exchange for the Company s contributions to the Discovery Collaboration, Roche will be required to make additional milestone and royalty payments.

In July 2007, the Company executed a common stock purchase agreement (the Common Stock Purchase Agreement) with Roche Finance Ltd, an affiliate of Roche (Roche Finance). Under the terms of the Common Stock Purchase Agreement, on August 9, 2007, Roche Finance purchased 1,975,000 shares of the Company s common stock at $21.50 per share, for an aggregate purchase price of $42.5 million. The Company recorded this issuance using the closing price of the Company s common stock on August 9, 2007, the date the shares were issued to Roche. Based on the closing price of $25.98, the fair value of the shares issued was $51.3 million, which was $8.8 million in excess of the proceeds received from Roche for the issuance of the Company s common stock. As a result, the Company allocated $8.8 million of the upfront payment from the LCA to the common stock issuance.

In connection with the execution of the LCA and the Common Stock Purchase Agreement, the Company also executed a share purchase agreement (the Alnylam Europe Purchase Agreement) with Alnylam Europe and Roche Beteiligungs GmbH, an affiliate of Roche Basel and Roche Finance (Roche Germany). Under the terms of the Alnylam Europe Purchase Agreement, which became effective in August 2007, the Company created a new, wholly-owned German limited liability company (Roche Kulmbach), into which substantially all of the non-intellectual property assets of Alnylam Europe were transferred, and Roche Germany purchased from the Company all of the issued and outstanding shares of Roche Kulmbach for an aggregate purchase price of $15.0 million. The Alnylam Europe Purchase Agreement also included transition services that were performed by Roche Kulmbach employees at various levels through August 2008. The Company reimbursed Roche for these services at an agreed-upon rate. The Company recorded as contra revenue (a reduction of revenues) $0.2 million and $1.0 million, respectively, for these services for the three and nine months ended September 30, 2008.

In addition, in connection with the closing of the Alnylam Europe Purchase Agreement, the Company granted restricted stock of the Company to certain employees of Roche Kulmbach. In connection with the closing, the Company also accelerated the unvested portion of the outstanding stock options of certain Alnylam Europe employees.

In summary, the Company received upfront payments totaling $331.0 million under the Roche alliance, which included an upfront payment under the LCA of $273.5 million, $42.5 million under the Common Stock Purchase Agreement and $15.0 million for the Roche Kulmbach shares under the Alnylam Europe Purchase Agreement.

The Company recorded $278.2 million as deferred revenue in connection with the Roche alliance. This amount represents the aggregate proceeds received from Roche of $331.0 million, net of the amount allocated to the common stock issuance of $51.3 million and the net book value of Alnylam Europe of $1.5 million.

When evaluating multiple element arrangements, the Company considers whether the components of the arrangement

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represent separate units of accounting as defined in EITF Issue No. 00-21, *Revenue Arrangements with Multiple Deliverables* (EITF 00-21). Application of this standard requires subjective determinations and requires management to make judgments about the value of each individual element and whether it is separable from the other aspects of the contractual relationship. The Company has determined that the deliverables under the Roche alliance include the license, the Alnylam Europe assets and employees, the steering committees (joint steering committee and future technology committee) and the services that the Company will be obligated to perform under the Discovery Collaboration. The Company has concluded that, pursuant to EITF 00-21, the license and assets of Alnylam Europe are not separable from the undelivered services (i.e., the steering committees and Discovery Collaboration) and, accordingly, the license and the services are being treated as a single unit of accounting. When multiple deliverables are accounted for as a single unit of accounting, the Company bases its revenue recognition pattern on the final deliverable. Under the Roche alliance, the steering committee services and the Discovery Collaboration services are the final deliverables and all such services will end, contractually, five years from the effective date of the LCA. The Company is recognizing the Roche-related revenue on a straight-line basis over five years because the Company cannot reasonably estimate the total level of effort required to complete its service obligations under the LCA. The Company will continue to reassess whether it can reasonably estimate the level of effort required to fulfill its obligations under the Roche alliance. In particular, when the Discovery Collaboration commences, the Company may be able to make such an estimate. When, and if, the Company can make a reasonable estimate of its remaining efforts under the collaboration, the Company would modify its method of recognition and utilize a proportional performance method. As future milestones are achieved, and to the extent they are within the five-year term, the amounts will be recognized as revenue prospectively over the remaining period of performance.

Takeda Alliance

In May 2008, the Company entered into a license and collaboration agreement (the Takeda Collaboration Agreement) with Takeda Pharmaceutical Company Limited (Takeda) to pursue the development and commercialization of RNAi therapeutics. Under the Takeda Collaboration Agreement, the Company granted Takeda a non-exclusive, worldwide, royalty-bearing license to the Company s intellectual property to develop, manufacture, use and commercialize RNAi therapeutics, subject to the Company s existing contractual obligations to third parties. The license initially is limited to the fields of oncology and metabolic disease and may be expanded at Takeda s option to include other therapeutic areas, subject to specified conditions. Under the Takeda Collaboration Agreement, Takeda will be the Company s exclusive platform partner in the Asian territory, as defined in the Takeda Collaboration Agreement, for a period of five years.

In consideration for the rights granted to Takeda under the Takeda Collaboration Agreement, Takeda agreed to pay the Company $150.0 million in upfront and near-term technology transfer payments. In addition, the Company has the option, exercisable until the start of Phase III development, to opt-in under a 50-50 profit sharing agreement to the development and commercialization in the United States of up to four Takeda licensed products, and would be entitled to opt-in rights for two additional products for each additional field expansion, if any, elected by Takeda under the Takeda Collaboration Agreement. In June 2008, Takeda paid the Company $100.0 million of the upfront payments. Takeda is also required to make an additional $50.0 million in payments to the Company upon achievement of specified technology transfer milestones, $20.0 million of which was achieved in September 2008 and paid in October 2008, $20.0 million of which is required to be paid within 12 to 24 months of execution of the Takeda Collaboration Agreement and $10.0 million of which is required to be paid within 24 to 36 months of execution of the Takeda Collaboration Agreement (collectively, the Technology Transfer Milestones). If Takeda elects to expand its license to additional therapeutic areas, Takeda will be required to pay the Company $50.0 million for each of up to approximately 20 total additional fields selected. In addition, Takeda is required to make payments to the Company upon achievement of development and commercialization milestones set forth in the Takeda Collaboration Agreement and royalty payments based on sales, if any, of RNAi therapeutic products by Takeda, its affiliates and sublicensees.

Pursuant to the Takeda Collaboration Agreement, the Company and Takeda have also agreed to collaborate on the research of RNAi therapeutics directed to one or two disease targets agreed to by the parties (the Research Collaboration), subject to the Company s existing contractual obligations with third parties. Takeda also has the option, subject to certain conditions, to collaborate with the Company on the research and development of RNAi drug

delivery technology for targets agreed to by the parties. In addition, Takeda has a right of first negotiation for the development and commercialization of the Company s RNAi therapeutic products in the Asian territory, excluding the Company s ALN-RSV01 program. In addition to the 50-50 profit sharing option, the Company has a similar right of first negotiation to participate with Takeda in the development and commercialization in the United States of licensed products. The collaboration between the Company and Takeda is governed by a joint technology transfer committee (the JTTC), a joint research collaboration committee (the JRCC) and a joint delivery collaboration committee (the JDCC), each of which is comprised of an equal number of representatives from each party.

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The Company has determined that the deliverables under the Takeda agreement include the license, the joint committees (the JTTC, JRCC and JDCC), the technology transfer activities and the services that the Company will be obligated to perform under the Research Collaboration. The Company has determined that, pursuant to EITF 00-21, the license and undelivered services (i.e., the joint committees and the Research Collaboration) are not separable and, accordingly, the license and services are being treated as a single unit of accounting.

When multiple deliverables are accounted for as a single unit of accounting, the Company bases its revenue recognition pattern on the final deliverable. Under the Takeda Collaboration Agreement, the last elements to be delivered are the JDCC and JTTC services, each of which has a finite life of no more than seven years. The Company is recognizing the upfront payment of $100.0 million, the first Technology Transfer Milestone of $20.0 million and the $30.0 million of remaining Technology Transfer Milestones on a straight-line basis over seven years because the Company is unable to reasonably estimate the level of effort to fulfill these obligations, primarily because the effort required under the Research Collaboration is largely unknown. As other milestones are achieved and the Company receives funding under the Research Collaboration, to the extent these events occur within the seven-year service period, the amounts will be recognized as revenue prospectively over the remaining period of performance. The Company will continue to reassess whether it can reasonably estimate the level of effort required to fulfill its obligations under the Takeda Collaboration Agreement. When, and if, the Company can make a reasonable estimate of its remaining efforts under the collaboration, the Company would modify its method of recognition and utilize a proportional performance method.

In addition, in connection with the Takeda Collaboration Agreement, the Company incurred $5.0 million of license fees payable to the Company s licensors, primarily Isis Pharmaceuticals, Inc. (Isis), during the second quarter of 2008, in accordance with the applicable license agreements with those parties. These fees were charged to research and development expense.

Novartis Broad Alliance

In the second half of 2005, the Company entered into a series of transactions with Novartis Pharma AG and its affiliate, Novartis Institutes for BioMedical Research, Inc. (collectively, Novartis). In September 2005, the Company and Novartis executed a stock purchase agreement (the Stock Purchase Agreement) and an investor rights agreement (the Investor Rights Agreement). In October 2005, in connection with the closing of the transactions contemplated by the Stock Purchase Agreement, the Investor Rights Agreement became effective and the Company and Novartis executed a research collaboration and license agreement (the Collaboration and License Agreement). The Collaboration and License Agreement has an initial term of three years, with an option for two additional one-year extensions at the election of Novartis. In July 2008, Novartis elected to extend the initial term for an additional year, through October 2009. Novartis retains the right to extend the term for a second additional year, which right must be exercised no later than July 2009.

Under the terms of the Stock Purchase Agreement, in October 2005, Novartis purchased 5,267,865 shares of the Company s common stock at a purchase price of $11.11 per share for an aggregate purchase price of $58.5 million, which, after such issuance, represented 19.9% of the Company s outstanding common stock as of the date of issuance. Under the Investor Rights Agreement, the Company granted Novartis rights to acquire additional equity securities such that Novartis would be able to maintain its then-current ownership percentage in the Company s outstanding common stock. Pursuant to terms of the Investor Rights Agreement, in May 2008, Novartis purchased 213,888 shares of the Company s common stock at a purchase price of $25.29 per share resulting in a payment to the Company of $5.4 million. At September 30, 2008, Novartis owned 13.2% of the Company s outstanding common stock.

Under the terms of the Collaboration and License Agreement, the parties will work together on a defined number of selected targets, as defined in the Collaboration and License Agreement, to discover and develop therapeutics based on RNAi. Novartis made upfront payments totaling $10.0 million to the Company in October 2005 in consideration for the rights granted to Novartis under the Collaboration and License Agreement and to reimburse prior costs incurred by the Company to develop *in vivo* RNAi technology. In addition, the Collaboration and License Agreement includes terms under which Novartis will provide the Company with research funding and milestone payments as well as royalties on annual net sales of products resulting from the Collaboration and License Agreement. The Collaboration and License Agreement also provides Novartis with a non-exclusive option to integrate the

Company s intellectual property relating to certain RNAi technology into Novartis operations under certain circumstances (the Integration Option), which Integration Option may be exercised during the term of our collaboration. In connection with the exercise of the Integration Option, Novartis will be required to make certain additional payments to the Company. The license grant under the Integration Option, if exercised, would be structured similarly to the Company s non-exclusive platform licenses with Roche and Takeda.

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The Company initially deferred the non-refundable $10.0 million upfront payment and the $6.4 million premium received from Novartis that represents the difference between the purchase price and the closing price of the common stock of the Company on the date of the stock purchase. These payments, in addition to research funding and certain milestone payments, are amortized into revenue using the proportional performance method over the estimated duration of the Collaboration and License Agreement, or ten years. Under this model, the Company estimates the level of effort to be expended over the term of the agreement and recognizes revenue based on the lesser of the amount calculated based on proportional performance of total expected revenue or the amount of non-refundable payments earned.

The Company believes the estimated term of the Collaboration and License Agreement includes the three-year term of the agreement, two one-year extensions at the election of Novartis, the first of which has been exercised by Novartis, and limited support as part of a technology transfer until the fifth anniversary of the termination of the agreement. Therefore, an expected term of ten years is used in the proportional performance model. The Company will evaluate the expected term when new information is known that could affect the Company s estimate. In the event the Company s period of performance is different than estimated, revenue recognition will be adjusted on a prospective basis.

Kyowa Hakko Alliance

In June 2008, the Company entered into a License and Collaboration Agreement (the Kyowa Hakko Agreement) with Kyowa Hakko Kogyo Co., Ltd. (Kyowa Hakko). Under the Kyowa Hakko Agreement, the Company granted Kyowa Hakko an exclusive license to its intellectual property in Japan and other major markets in Asia (the Licensed Territory) for the development and commercialization of ALN-RSV01, an RNAi therapeutic for the treatment of respiratory syncytial virus (RSV) infection, for which the Company is currently conducting Phase II clinical trials. The Kyowa Hakko Agreement also covers additional RSV-specific RNAi therapeutic compounds that comprise the ALN-RSV program (Additional Compounds). The Company retains all development and commercialization rights worldwide excluding the Licensed Territory.

Under the terms of the Kyowa Hakko Agreement, in June 2008, Kyowa Hakko paid the Company an upfront cash payment of $15.0 million. In addition, Kyowa Hakko is required to make payments to the Company upon achievement of specified development and sales milestones set forth in the Kyowa Hakko Agreement and royalty payments based on annual net sales, if any, of ALN-RSV01 by Kyowa Hakko, its affiliates and sublicenses in the Licensed Territory.

The collaboration between Kyowa Hakko and the Company is governed by a joint steering committee that is comprised of an equal number of representatives from each party. Under the agreement, Kyowa Hakko is establishing a development plan for ALN-RSV01 relating to the development activities to be undertaken in the Licensed Territory, with the initial focus on Japan. Kyowa Hakko is responsible, at its expense, for all development activities under the development plan that are reasonably necessary for the regulatory approval of ALN-RSV01 in Japan, as well as for the regulatory approval and commercialization of the product in the Licensed Territory. The Company will be responsible for supply of the product to Kyowa Hakko under a supply agreement unless Kyowa Hakko elects, prior to the first commercial sale of the product in the Licensed Territory, to manufacture the product itself or arrange for a third party to manufacture the product.

The Company has determined that the deliverables under the Kyowa Hakko Agreement include the license, the joint steering committee, the manufacturing services and any Additional Compounds. The Company has determined that, pursuant to EITF 00-21, the individual deliverables are not separable and, accordingly, must be accounted for as a single unit of accounting.

When multiple deliverables are accounted for as a single unit of accounting, the Company bases its revenue recognition pattern on the final deliverable. The Company is currently unable to reasonably estimate its period of performance under the Kyowa Hakko Agreement, as it is unable to estimate the timeline of its deliverables related to the fixed-price option granted to Kyowa Hakko for any Additional Compounds. The Company is deferring all revenue under the Kyowa Hakko Agreement until it is able to reasonably estimate its period of performance. The Company will continue to reassess whether it can reasonably estimate the period of performance to fulfill its obligations under the Kyowa Hakko Agreement.

NIH Contract

In September 2006, the Company was awarded a contract to advance the development of a broad spectrum RNAi anti-viral therapeutic for hemorrhagic fever viruses, including the Ebola virus, with the National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health (NIH). The federal contract could provide the Company with up to $23.0 million in funding over a four-year period to develop RNAi therapeutics as anti-viral drugs targeting the Ebola virus. Of the

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$23.0 million in funding, the government initially committed to pay the Company up to $14.2 million over the first two years of the contract and, in June 2008, as a result of the progress of the program, the government awarded the Company an additional $7.5 million, to be paid through September 2009 for the third year of the contract. Revenue under government cost reimbursement contracts is recognized as the Company performs the underlying research and development activities.

Department of Defense Contract

In August 2007, the Company was awarded a contract to advance the development of a broad spectrum RNAi anti-viral therapeutic for hemorrhagic fever virus with the Defense Threat Reduction Agency (DTRA) of the United States Department of Defense. The federal contract could provide the Company with up to $38.6 million in funding through February of 2011 to develop RNAi therapeutics for hemorrhagic fever virus infection. Of the $38.6 million in funding, the government has committed to pay the Company up to $10.9 million through February 2009, which term includes a six-month extension granted by DTRA in July 2008. Subject to the progress of the program and budgetary considerations in future years, the remaining $27.7 million may be paid over the last two years of the contract. Revenue under government cost reimbursement contracts is recognized as the Company performs the underlying research and development activities.

4. DELIVERY TECHNOLOGY

The Company is working to extend its capabilities in developing technology to achieve efficacious and safe delivery of RNAi therapeutics to a broad spectrum of organ and tissue types. In connection with these efforts, the Company has entered into a number of agreements to evaluate and gain access to certain delivery technologies. In some instances, the Company is also providing funding to support the advancement of these delivery technologies.

In January 2007, the Company obtained an exclusive worldwide license to the liposomal delivery formulation technology of Tekmira Pharmaceuticals Corporation (Tekmira), formerly known as Inex Pharmaceuticals Corporation, for the discovery, development and commercialization of lipid-based nanoparticle formulations for the delivery of RNAi therapeutics. In connection with its original agreement with Tekmira, the Company issued to Tekmira 361,990 shares of common stock. These shares had a value of $7.9 million at the time of issuance, which amount was expensed during the first quarter of 2007. In May 2008, Tekmira acquired Protiva Biotherapeutics, Inc. (Protiva). In connection with this acquisition, the Company entered into new agreements with Tekmira and Protiva which provide the Company with access to key existing and future technology and intellectual property for the systemic delivery of RNAi therapeutics with liposomal delivery technologies. In addition, the Company made an equity investment of $5.0 million in Tekmira, purchasing 2,083,333 shares of Tekmira common stock at a price of $2.40 per share, which represented a premium of $1.00 per share, or an aggregate of $2.1 million. This premium was calculated as the difference between the purchase price and the closing price of Tekmira s common stock on the effective date of the acquisition. The Company allocated this $2.1 million premium to the expansion of the Company s access to key technology and intellectual property rights and, accordingly, recorded a charge to research and development expense during the second quarter of 2008. The Company recorded this investment as an available-for-sale security in marketable securities on its condensed consolidated balance sheets. During the three months ended September 30, 2008, the Company recorded an impairment charge of $1.6 million related to its investment in Tekmira, as the decrease in the fair value of this investment was deemed to be other than temporary.

5. INCOME TAXES

During the three and nine months ended September 30, 2008, the Company recorded a benefit from income taxes of $0.8 million and a provision for income taxes of $0.7 million, respectively. The Company provides income tax expense for federal alternative minimum tax, state and foreign taxes. The Company is generating U.S. taxable income during 2008 due to the recognition of certain proceeds received from the Roche alliance. The Company s U.S. taxable income is expected to be offset by net operating loss carry forwards and other deferred tax attributes. However, the Company will continue to be subject to federal alternative minimum tax and state income taxes.

During the three months ended September 30, 2008, the Company discovered that it had overstated its state income tax provision by $0.9 million during the six months ended June 30, 2008. To correct its income tax provision, the Company recorded a credit to income taxes of $0.9 million in the three months ended September 30, 2008, resulting in a net income tax benefit of $0.8 million in the three months ended September 30, 2008 and a tax provision

of $0.7 million for the nine months ended September 30, 2008.

The Company continues to maintain a full valuation allowance against its net deferred tax assets due to the uncertainty of realizing such benefits. At December 31, 2007, the Company had federal and state net operating loss carryforwards of $138.3 million

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and $161.8 million, respectively, available to reduce future taxable income, that will expire at various dates beginning in 2008 through 2027. At December 31, 2007, federal and state research and development and other credit carryforwards, available to reduce future tax liabilities, were $3.4 million and $2.1 million, respectively, and expire at various dates beginning in 2018 through 2027. At December 31, 2007, foreign tax credits, available to reduce future tax liabilities, were $3.1 million and expire in 2017. Ownership changes, as defined in the Internal Revenue Code, including those resulting from the issuance of common stock in connection with the Company s public offerings, may limit the amount of net operating loss and tax credit carryforwards that can be utilized to offset future taxable income or tax liability. The amount of the limitation is determined in accordance with Section 382 of the Internal Revenue Code.

On January 1, 2007, the Company adopted the provisions of FASB Interpretation No. 48, "*Accounting for Uncertainty in Income Taxes an interpretation of FASB Statement 109* (FIN 48), which was issued in July 2006. The implementation of FIN 48 did not result in any adjustment to the Company s beginning tax positions. The Company continues to recognize fully its tax benefits which are offset by a valuation allowance to the extent that it is more likely than not that the deferred tax assets will not be realized. At September 30, 2008, the Company did not have any unrecognized tax benefits.

6. INVESTMENT IN JOINT VENTURE (REGULUS THERAPEUTICS LLC)

In September 2007, the Company entered into a joint venture with Isis to create a new Delaware limited liability company, Regulus Therapeutics, to focus on the discovery, development and commercialization of microRNA therapeutics, a potential new class of drugs to treat the pathways of human disease. The Company and Isis own 49% and 51%, respectively, of Regulus Therapeutics.

Under the terms of the limited liability company agreement among the Company, Isis and Regulus Therapeutics (the LLC Agreement), Regulus Therapeutics is operated as an independent company and governed by a managing board comprised of an equal number of directors appointed by each of the Company and Isis. In consideration for the Company s and Isis initial interests in Regulus Therapeutics, each party granted Regulus Therapeutics exclusive licenses to its intellectual property for certain microRNA therapeutic applications as well as certain patents in the microRNA field. In addition, the Company made an initial cash contribution to Regulus Therapeutics of $10.0 million, resulting in the Company and Isis making approximately equal aggregate initial capital contributions to Regulus Therapeutics.

In connection with the execution of the LLC Agreement, the Company, Isis and Regulus Therapeutics entered into a license and collaboration agreement (the Regulus Therapeutics Collaboration Agreement) to pursue the discovery, development and commercialization of therapeutic products directed to microRNAs. The Company also executed a services agreement (the Services Agreement) with Isis and Regulus Therapeutics. Under the terms of the Services Agreement, the Company and Isis provide to Regulus Therapeutics certain research and development and general and administrative services for which they generally are paid by Regulus Therapeutics.

In April 2008, Regulus Therapeutics entered into a worldwide strategic alliance with GlaxoSmithKline (GSK) to discover, develop and commercialize up to four novel microRNA-targeted therapeutics to treat inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. In connection with this alliance, Regulus Therapeutics received $20.0 million in upfront payments from GSK, including a $15.0 million option fee and a loan of $5.0 million evidenced by a promissory note (guaranteed by Isis and the Company) that will convert into Regulus Therapeutics common stock under certain specified circumstances. Regulus Therapeutics could be eligible to receive development, regulatory and sales milestone payments for each of the microRNA-targeted therapeutics discovered and developed as part of the alliance. Regulus Therapeutics would also receive royalty payments on worldwide sales of products resulting from the alliance.

The Company has concluded that Regulus Therapeutics qualifies as a variable interest entity under FASB Interpretation No. 46R, *Consolidation of Variable Interest Entities an interpretation of Accounting Research Bulletin No. 51* (FIN 46R). The LLC Agreement contains transfer restrictions on each of Isis and the Company s LLC interests and, as a result, Isis and the Company are considered related parties under paragraph 16(d)(1) of FIN 46R. The Company has assessed which entity would be considered the primary beneficiary under FIN 46R and has concluded that Isis is the primary beneficiary and, accordingly, the Company has not consolidated Regulus

Therapeutics.

The Company accounts for its investment in Regulus Therapeutics using the equity method of accounting. The Company is recognizing the first $10.0 million of losses of Regulus Therapeutics as equity in loss of joint venture (Regulus Therapeutics LLC) in its condensed consolidated statements of operations because the Company is responsible for funding those losses through its initial $10.0 million cash contribution. Thereafter, the Company will recognize 49% of the income and losses of Regulus Therapeutics. Under the equity

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method, the reimbursement of expenses to the Company is recorded as a reduction to research and development expenses. At September 30, 2008, the Company s investment in the joint venture was $4.7 million, which is recorded as an investment in joint venture (Regulus Therapeutics LLC) in the condensed consolidated balance sheets under the equity method. The results of Regulus Therapeutics operations for the three and nine months ended September 30, 2008 and 2007 are presented in the table below, in thousands:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2008	2007	2008	2007
Statement of Operations Data:				
Net revenues	$ 681	$ 41	$ 1,429	$ 41
Operating expenses (1)	3,214	245	7,883	245
Loss from operations	(2,533)	(204)	(6,454)	(204)
Other income	68	26	217	26
Net loss	$ (2,465)	$ (178)	$ (6,237)	$ (178)
(1) Non-cash stock-based compensation included in operating expenses	$ 752	$ 80	$ 1,808	$ 80

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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 and Section 21E of the Securities Exchange Act of 1934. Without limiting the foregoing, the words may, will, should, could, expects, plans, intends, anticipates, believes, estimates, predicts, potential, continue, target and similar expressions are intended to identify forward-looking statements. 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 assume no obligation to update any such forward-looking statements. 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 below under this Item 2 Management s Discussion and Analysis of Financial Condition and Results of Operations, 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 expect to apply in a systematic way to develop RNAi therapeutics for a variety of diseases.

We are applying our technological expertise to build a pipeline of RNAi therapeutics to address significant medical needs, many of which cannot effectively be addressed with small molecules or antibodies, the current major classes of drugs. Our lead RNAi therapeutic program, ALN-RSV01, is in Phase II clinical trials for the treatment of human respiratory syncytial virus, or RSV, infection, which is reported to be the leading cause of hospitalization in infants in the United States and also occurs in the elderly and in immune compromised adults. We submitted an investigational new drug application, or IND, for ALN-RSV01 to the United States Food and Drug Administration, or FDA, in November 2005, and have completed a number of Phase I clinical trials carried out in both the United States and Europe. In these Phase I trials, ALN-RSV01 was found to be safe and well tolerated when administered intranasally or by nebulizer. In February 2008, we reported positive results from our Phase II experimental infection clinical trial, referred to as the GEMINI study. The GEMINI study was designed to evaluate the safety, tolerability and anti-viral activity of ALN-RSV01. In this study, ALN-RSV01 was found to be safe and well tolerated and demonstrated statistically significant anti-viral activity, including an approximately 40% reduction in viral infection and a 95% increase in infection-free patients ($p<0.01$), as compared to placebo. The results of our completed ALN-RSV01 clinical trials have been presented at medical conferences. In April 2008, we initiated a second Phase II human clinical trial, which is currently ongoing, to assess the safety and tolerability of aerosolized ALN-RSV01 versus placebo in adult lung transplant patients naturally infected with RSV.

We are also working on a number of programs in pre-clinical development, including:

- ALN-VSP, a dual-acting RNAi therapeutic we are developing for the treatment of liver cancers and potentially other solid tumors, which is designed to target both vascular endothelial growth factor, or VEGF, and kinesin spindle protein, or KSP;

- ALN-PCS, an RNAi therapeutic targeting a gene called proprotein convertase subtilisin/kexin type 9, or PCSK9, for the treatment of hypercholesterolemia;

ALN-HTT, an RNAi therapeutic for the treatment of Huntington s disease, which we are developing in collaboration with Medtronic, Inc., or Medtronic; and

ALN-TTR, an RNAi therapeutic targeting the transthyretin, or TTR, gene, for the treatment of TTR amyloidosis.

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We have pre-clinical discovery programs for RNAi therapeutics for the treatment of a broad range of diseases, including viral hemorrhagic fever, including the Ebola virus, progressive multifocal leukoencephalopathy, or PML, a CNS disease caused by viral infection in immune compromised patients, pandemic flu, Parkinson s disease and cystic fibrosis, an inherited respiratory disease, or CF, several other diseases that are the subject of our strategic alliances, as well as other undisclosed programs.

We also are working internally and with third-party collaborators to develop the capabilities to deliver our RNAi therapeutics directly to specific sites of disease, such as the delivery of ALN-RSV01 to the lungs, which we refer to as Direct RNAi . In addition, we are working to extend our capabilities to advance the development of RNAi therapeutics that are administered by intravenous, subcutaneous or intramuscular approaches, which we refer to as Systemic RNAi . For example, in May of 2007, we entered into an agreement with the Massachusetts Institute of Technology, or MIT, Center for Cancer Research under which we are sponsoring an exclusive five-year research program focused on the delivery of RNAi therapeutics.

In addition, during 2007, we obtained an exclusive worldwide license to the liposomal delivery formulation technology of Tekmira Pharmaceuticals Corporation, or Tekmira, formerly known as Inex Pharmaceuticals Corporation, for the discovery, development and commercialization of lipid-based nanoparticle formulations for the delivery of RNAi therapeutics. In May 2008, Tekmira acquired Protiva Biotherapeutics, Inc., or Protiva. In connection with this acquisition, we entered into new agreements with Tekmira and Protiva, which provide us access to key existing and future technology and intellectual property for the systemic delivery of RNAi therapeutics with liposomal delivery technologies. Under the new agreements with Tekmira and Protiva, we continue to have exclusive rights to the Semple (U.S. Patent No. 6,858,225) and Wheeler (U.S. Patent Nos. 5,976,567 and 6,815,432) patents, which we believe are critical for the use of cationic liposomal delivery technology. In connection with these new agreements, we granted the combined entity InterfeRx licenses to discover, develop and commercialize RNAi therapeutics towards seven gene targets, a number that includes three previously announced InterfeRx licenses granted to Tekmira as part of its January 2007 agreement. In return for these licenses, we are eligible to receive milestone fees and royalties on future targets, if any. Under these agreements, we have retained the option to co-develop and co-commercialize any products targeting polo-like kinase 1, or PLK1, one of the seven gene targets for which we have granted the new company an InterfeRx license, for the treatment of certain cancers. The PLK1 gene has been shown to be involved in the growth of certain types of solid tumors.

As noted above, we are developing ALN-VSP, a systemically delivered RNAi therapeutic, for the treatment of liver cancers and potentially other solid tumors. ALN-VSP comprises two siRNAs formulated using SNALP technology. We also have rights to use SNALP technology in the advancement of our other systemically delivered RNAi therapeutic programs, including ALN-PCS for the treatment of hypercholesterolemia.

In connection with Tekmira s acquisition of Protiva, in May 2008 we made an equity investment of $5.0 million in Tekmira, purchasing 2,083,333 shares of Tekmira common stock at a price of $2.40 per share, which represented a premium of $1.00 per share, or an aggregate of $2.1 million. This premium was calculated on the difference between the purchase price and the closing price of Tekmira s common stock on the effective date of the acquisition. We allocated this $2.1 million premium to the expansion of our access to key technology and intellectual property rights and, accordingly, recorded a charge to research and development expense during the second quarter of 2008. During the three months ended September 30, 2008, we recorded an impairment charge of $1.6 million related to our investment in Tekmira, as the decrease in the fair value of this investment was deemed to be other than temporary.

We have other RNAi therapeutic delivery collaborations and intend to continue to collaborate with academic and corporate third parties to evaluate different delivery options, including with respect to Direct RNAi and Systemic RNAi.

We rely on the strength of our intellectual property portfolio relating to the development and commercialization of small interfering RNAs, or siRNAs, as therapeutics. This includes ownership of, or exclusive rights to, issued patents and pending patent applications claiming fundamental features of siRNAs and RNAi therapeutics. We believe that no other company possesses a portfolio of such broad and exclusive rights to the fundamental RNAi patents and patent applications required for the development and 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 any challenges that have arisen or may arise in this area.

In addition, our expertise in RNAi therapeutics and broad intellectual property estate have enabled us to form alliances with leading companies, including F. Hoffmann-La Roche Ltd, or Roche, Takeda Pharmaceutical Company Limited, or Takeda, Novartis Pharma AG, or Novartis, Medtronic, Kyowa Hakko Kogyo Co., Ltd., or Kyowa Hakko, and Biogen Idec Inc., or Biogen Idec. In addition, we have entered into contracts with government agencies, including the National Institute of Allergy and Infectious Diseases,

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or NIAID, a component of the National Institutes of Health, or NIH, and the Defense Threat Reduction Agency, or DTRA, an agency of the United States Department of Defense, or DoD. We have established collaborations with and, in some instances, received funding from, a number of major medical and disease associations, including The University of Texas Southwestern Medical Center, or UTSW, the Mayo Clinic, The Michael J. Fox Foundation and the Cystic Fibrosis Foundation Therapeutics, or CFTT.

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.

In May 2008, we entered into a license and collaboration agreement with Takeda to pursue the development and commercialization of RNAi therapeutics. Under the Takeda agreement, we granted to Takeda a non-exclusive, worldwide, royalty-bearing license to our intellectual property to develop, manufacture, use and commercialize RNAi therapeutics, subject to our existing contractual obligations to third parties. The license initially is limited to the fields of oncology and metabolic disease and may be expanded at Takeda s option to include other therapeutic areas, subject to specified conditions. In consideration for the rights granted to Takeda under the Takeda agreement, Takeda agreed to pay us $150.0 million in upfront and near-term technology transfer payments. In addition, we have the option, exercisable until the start of Phase III development, to opt-in under a 50-50 profit sharing agreement to the development and commercialization in the United States of up to four Takeda licensed products, and would be entitled to opt-in rights for two additional products for each additional field expansion, if any, elected by Takeda under the Takeda agreement. In June 2008, Takeda paid us $100.0 million in upfront payments and is required to make an additional $50.0 million in near-term payments to us upon achievement of specified technology transfer milestones, $20.0 million of which was achieved in September 2008 and paid in October 2008, $20.0 million of which is required to be paid within 12 to 24 months of execution of the agreement and $10.0 million of which is required to be paid within 24 to 36 months of execution of the agreement. If Takeda elects to expand its license to additional therapeutic areas, Takeda will be required to pay us $50.0 million for each of up to approximately 20 total additional fields selected. In addition, Takeda is required to make payments to us upon achievement of development and commercialization milestones set forth in the Takeda agreement, and royalty payments based on sales, if any, of RNAi therapeutic products by Takeda, its affiliates and sublicensees. A more complete description of the Takeda agreement is set forth below under Strategic Alliances.

In June 2008, we entered into a license and collaboration agreement with Kyowa Hakko under which we granted Kyowa Hakko an exclusive license to our intellectual property in Japan and other major markets in Asia for the development and commercialization of ALN-RSV01 for the treatment of RSV infection. The Kyowa Hakko agreement also covers additional RSV-specific RNAi therapeutic compounds that comprise the ALN-RSV program. We retain all development and commercialization rights worldwide excluding the licensed territory. Under the terms of the Kyowa Hakko agreement, Kyowa Hakko paid us an upfront cash payment of $15.0 million. In addition, Kyowa Hakko is required to make payments to us upon achievement of specified development and sales milestones set forth in the Kyowa Hakko agreement, and royalty payments based on annual net sales, if any, of ALN-RSV01 by Kyowa Hakko, its affiliate and sublicenses in the licensed territory. A more complete description of the Kyowa Hakko agreement is set forth below under Strategic Alliances.

In July 2008, Novartis elected to extend the initial three-year term of our collaboration and license agreement for an additional year, through October 2009. Under the term of the Novartis agreement, Novartis has the option to extend for one additional year following this extension, which right must be exercised no later than July 2009.

In September 2007, we and Isis Pharmaceuticals, Inc., or Isis, established Regulus Therapeutics LLC, or Regulus Therapeutics, a joint venture focused on the discovery, development and commercialization of microRNA therapeutics. Because microRNAs are believed to regulate whole networks of genes that can be involved in discrete disease processes, microRNA therapeutics represent a possible new approach to target the pathways of human disease. Regulus Therapeutics combines our and Isis technologies, know-how and intellectual property relating to microRNA therapeutics. We believe Regulus Therapeutics has assembled a strong leadership team, as well as leading authorities in the field of microRNA research to lead this new venture.

In addition, we recently expanded our technology platform with the acquisition of RNA activation, or RNAa, technology. As part of our overall strategy to be the leader in the field of RNA therapeutics, including RNAi and microRNA therapeutics, we consolidated key intellectual property in the emerging biological field of RNAa. RNAa technology has the potential to activate gene expression, which may have multiple potential therapeutic applications, including certain genetic diseases and cancer. We have entered into exclusive license agreements with UTSW, University of California San Francisco and the Salk Institute for Biological Studies. RNAa technology represents a potential new product platform in our efforts to advance innovative medicines to patients.

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Alnylam commenced operations in June 2002. We have focused our efforts since inception primarily on business planning, research and development, acquiring, filing and expanding intellectual property rights, recruiting management and technical staff, and raising capital. Since our inception, we have generated significant losses. As of September 30, 2008, we had an accumulated deficit of $242.9 million. Through September 30, 2008, we have funded our operations primarily through the net proceeds from the sale of equity securities and payments we have received under strategic alliances. Through September 30, 2008, a substantial portion of our total net revenues have been collaboration revenues derived from our strategic alliances with Roche, Takeda, Novartis and Merck & Co., Inc., or Merck, and from the United States government in connection with our development of treatments for hemorrhagic fever viruses, including Ebola. We expect our revenues to continue to be derived primarily from new and existing strategic alliances, government and foundation funding and license fee revenues.

We currently have programs focused in a number of therapeutic areas. However, we are unable to predict when, if ever, we will successfully develop or be able to commence sales of any product. We have never achieved profitability on an annual basis and we expect to incur additional losses over the next several years. We expect our net losses to continue primarily due to research and development activities relating to our drug development programs, collaborations and other general corporate activities. 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. Our sources of potential funding for the next several years are expected to be derived primarily from payments under new and existing strategic alliances, which may include license and other fees, funded research and development payments and milestone payments, government and foundation funding and proceeds from the sale of equity.

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. Our most advanced program is focused on the treatment of RSV infection. Our other development programs are focused on the treatment of liver cancers and potentially other solid tumors, hypercholesterolemia, Huntington s disease and TTR amyloidosis. We also have discovery programs to develop RNAi therapeutics for the treatment of a broad range of diseases, such as viral hemorrhagic fever, including the Ebola virus, PML, pandemic flu, Parkinson s disease, CF, several other diseases that are the subject of our strategic alliances, and other undisclosed programs. In addition, we are working internally and with third-party collaborators to develop capabilities to deliver our RNAi therapeutics both directly to the specific sites of disease and systemically, and we intend to continue to collaborate with academic and corporate third parties to evaluate different delivery options.

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 progress product candidates into pre-clinical and clinical trials;
- the scope, rate and progress 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 collaborative, licensing and other arrangements that we may establish;

the cost, timing and success of regulatory filings and approvals;

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

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

the effect of competing technological and market developments.

Any failure to complete any stage of the development or commercialization 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 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 pharmaceutical and biotechnology companies, academic institutions, research foundations and others, as appropriate, to gain access to funding, technical resources and intellectual property to further our development efforts and to generate revenues. We have entered into license agreements with Max Planck Innovation, Tekmira, MIT and Isis, as well as a number of other entities, to obtain rights to important intellectual property in the field of RNAi. In addition, our collaboration strategy is to form (1) non-exclusive platform alliances where our collaborators obtain access to our capabilities and intellectual property to develop their own RNAi therapeutic products and (2) 50/50 co-development and/or ex-U.S. market geographic collaborations on specific RNAi therapeutic programs. We have entered into broad, non-exclusive platform license agreements with Roche and Takeda, under which we will also collaborate with each of Roche and Takeda on RNAi drug discovery for one or more disease targets. We also have discovery and development alliances with Novartis, Biogen Idec and Medtronic. Two of the programs we are pursuing under our alliances with Novartis and Medtronic are 50/50 co-development programs. In addition, we have entered into a license and collaboration agreement with Kyowa Hakko, under which we granted Kyowa Hakko an exclusive license to our intellectual property in Japan and other major markets in Asia for the development and commercialization of ALN-RSV01 for the treatment of RSV infection.

We have also entered into contracts with government agencies, including NIAID and DTRA. We have established collaborations with and, in some instances, received funding from, a number of major medical and disease associations including UTSW, the Mayo Clinic, The Michael J. Fox Foundation and the CFTT. 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 under our InterfeRx program and to research companies that commercialize RNAi reagents or services under our research product licenses. As of October 31, 2008, we had granted such licenses, on either an exclusive or nonexclusive basis, to approximately 20 companies, and options to take such licenses to two additional companies.

Takeda Alliance. In May 2008, we entered into a license and collaboration agreement with Takeda to pursue the development and commercialization of RNAi therapeutics. Under the Takeda agreement, we granted to Takeda a non-exclusive, worldwide, royalty-bearing license to our intellectual property to develop, manufacture, use and commercialize RNAi therapeutics, subject to our existing contractual obligations to third parties. The license initially is limited to the fields of oncology and metabolic disease and may be expanded at Takeda s option to include other therapeutic areas, subject to specified conditions. Under the Takeda agreement, Takeda will be our exclusive platform partner in the Asian territory, as defined in the agreement, for a period of five years.

In consideration for the rights granted to Takeda under the Takeda agreement, Takeda agreed to pay us $150.0 million in upfront and near-term technology transfer payments. In addition, we have the option, exercisable until the start of Phase III development, to opt-in under a 50-50 profit sharing agreement to the development and commercialization in the United States of up to four Takeda licensed products, and would be entitled to opt-in rights for two additional products for each additional field expansion, if any, elected by Takeda under the Takeda agreement. In June 2008, Takeda paid us $100.0 million of the upfront payments. Takeda is also required to make an additional $50.0 million in payments to us upon achievement of specified technology transfer milestones, $20.0 million of which was achieved in September 2008 and paid in October 2008, $20.0 million of which is required to be paid within 12-24 months of execution of the agreement and $10.0 million of which is required to be paid within 24-36 months of execution of the agreement. If Takeda elects to expand its license to additional therapeutic areas, Takeda will be

required to pay us $50.0 million for each of up to approximately 20 total additional fields selected. In addition, Takeda is required to make payments to us upon achievement of development and commercialization milestones set forth in the Takeda agreement and royalty payments based on sales, if any, of RNAi therapeutic products by Takeda, its affiliates and sublicensees.

Pursuant to the Takeda agreement, we and Takeda have also agreed to collaborate on the research of RNAi therapeutics directed to one or two disease targets agreed to by the parties, subject to our existing contractual obligations with third parties. Takeda also has the option, subject to certain conditions, to collaborate with us on the research and development of RNAi drug delivery

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technology for targets agreed to by the parties. In addition, Takeda has a right of first negotiation for the development and commercialization of our RNAi therapeutic products in the Asian territory, excluding our ALN-RSV01 program. In addition to our 50-50 profit sharing option, we have a similar right of first negotiation to participate with Takeda in the development and commercialization in the United States of licensed products. The collaboration is governed by a joint technology transfer committee, or JTTC, a joint research collaboration committee, or JRCC, and a joint delivery collaboration committee, or JDCC, each of which is comprised of an equal number of representatives from each party.

The term of the Takeda agreement generally ends upon the later of (i) the expiration of our last-to-expire patent covering a licensed product and (ii) the last-to-expire term of a profit sharing agreement in the event we elect to enter into such an agreement. The Takeda agreement may be terminated by either party in the event the other party fails to cure a material breach under the agreement. In addition, after the first anniversary of the effective date of the Takeda agreement, Takeda may terminate the agreement on a licensed product-by-licensed product or country-by-country basis upon 180-days prior written notice to us provided, however, that Takeda is required to continue to make royalty payments to us for the duration of the royalty term with respect to a licensed product.

We have determined that the deliverables under the Takeda agreement include the license, the joint committees (the JTTC, JRCC and JDCC), the technology transfer activities and the services that we will be obligated to perform under the research collaboration with Takeda. We have determined that, pursuant to Emerging Issues Task Force, or EITF, Issue No. 00-21, Revenue Arrangements with Multiple Deliverables, or EITF 00-21, the license and undelivered services (i.e., the joint committees and the research collaboration) are not separable and, accordingly, the license and services are being treated as a single unit of accounting.

When multiple deliverables are accounted for as a single unit of accounting, we base our revenue recognition pattern on the final deliverable. Under the Takeda agreement, the last elements to be delivered are the JDCC and JTTC services, each of which has a finite life of no more than seven years. We are recognizing the upfront payment of $100.0 million, the first technology transfer milestone of $20.0 million and the remaining $30.0 million of technology transfer milestones on a straight-line basis over seven years because we are unable to reasonably estimate the level of effort to fulfill these obligations, primarily because the effort required under the research collaboration is largely unknown. As future milestones are achieved and we receive funding under the research collaboration, to the extent these events are within the seven-year service period, the amounts will be recognized as revenue prospectively over the remaining period of performance. We will continue to reassess whether we can reasonably estimate the level of effort required to fulfill our obligations under the Takeda agreement. When, and if, we can make a reasonable estimate of our remaining efforts under the collaboration, we would modify our method of recognition and utilize a proportional performance method.

In addition, in connection with the Takeda agreement, we incurred $5.0 million of license fees payable to our licensors, primarily Isis, during the second quarter of 2008, in accordance with the applicable license agreements with those parties. These fees were charged to research and development expense.

Kyowa Hakko Alliance. In June 2008, we entered into a license and collaboration agreement with Kyowa Hakko. Under the Kyowa Hakko agreement, we granted Kyowa Hakko an exclusive license to our intellectual property in Japan and other major markets in Asia for the development and commercialization of ALN-RSV01 for the treatment of RSV infection. The Kyowa Hakko agreement also covers additional RSV-specific RNAi therapeutic compounds that comprise the ALN-RSV program. We retain all development and commercialization rights worldwide excluding the licensed territory.

Under the terms of the Kyowa Hakko agreement, in June 2008, Kyowa Hakko paid us an upfront cash payment of $15.0 million. In addition, Kyowa Hakko is required to make payments to us upon achievement of specified development and sales milestones set forth in the Kyowa Hakko agreement, and royalty payments based on annual net sales, if any, of ALN-RSV01 by Kyowa Hakko, its affiliates and sublicenses in the licensed territory.

Our collaboration with Kyowa Hakko is governed by a joint steering committee that is comprised of an equal number of representatives from each party. Under the agreement, Kyowa Hakko is establishing a development plan for ALN-RSV01 relating to the development activities to be undertaken in the licensed territory, with the initial focus on Japan. Kyowa Hakko is responsible, at its expense, for all development activities under the development plan that are reasonably necessary for the regulatory approval of ALN-RSV01 in Japan, as well as for the regulatory approval

and commercialization of the product in the licensed territory. We will be responsible for supply of the product to Kyowa Hakko under a supply agreement unless Kyowa Hakko elects, prior to the first commercial sale of the product in the licensed territory, to manufacture the product itself or arrange for a third party to manufacture the product.

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The term of the Kyowa Hakko agreement generally ends on a country-by-country basis upon the later of (i) the expiration of our last-to-expire patent covering a licensed product and (ii) the tenth anniversary of the first commercial sale in the country of sale. The Kyowa Hakko agreement may be terminated by either party in the event the other party fails to cure a material breach under the agreement. In addition, Kyowa Hakko may terminate the agreement without cause upon 180-days prior written notice to us, subject to certain conditions.

We have determined that the deliverables under the Kyowa Hakko agreement include the license, the joint steering committee, the manufacturing services and any additional RSV-specific RNAi therapeutic compounds that comprise the ALN-RSV program. We have determined that pursuant to EITF 00-21, the individual deliverables are not separable and, accordingly, must be accounted for as a single unit of accounting. When multiple deliverables are accounted for as a single unit of accounting, we base our revenue recognition pattern on the final deliverable. We are currently unable to reasonably estimate our period of performance under the Kyowa Hakko agreement, as we are unable to estimate the timeline of our deliverables related to the fixed-price option granted to Kyowa Hakko for any additional compounds. We are deferring all revenue under the Kyowa Hakko agreement until we are able to reasonably estimate our period of performance. We will continue to reassess whether we can reasonably estimate the period of performance to fulfill our obligations under the Kyowa Hakko agreement.

Joint Venture (Regulus Therapeutics LLC)

In September 2007, we and Isis established Regulus Therapeutics, a joint venture focused on the discovery, development and commercialization of microRNA therapeutics. Because microRNAs are believed to regulate whole networks of genes that can be involved in discrete disease processes, microRNA therapeutics represent a new approach to target the pathways of human disease. We and Isis own 49% and 51%, respectively, of Regulus Therapeutics. Regulus Therapeutics is operated as an independent company with a separate board of directors, scientific advisory board and management team. In connection with the execution of the limited liability company agreement, we, Isis and Regulus Therapeutics entered into a license and collaboration agreement to pursue the discovery, development and commercialization of therapeutic products directed to microRNAs. We made an initial cash contribution to Regulus Therapeutics of $10.0 million, resulting in us and Isis making initial capital contributions to Regulus Therapeutics of approximately equal aggregate value.

Regulus Therapeutics most advanced program is a microRNA therapeutic that targets miR-122 for the treatment of hepatitis C virus, or HCV, infection, a significant disease worldwide for which emerging therapies target viral genes and, therefore, are prone to viral resistance. In addition to the miR-122 program, Regulus Therapeutics is also actively exploring additional areas for development of microRNA therapeutics, including cancer, other viral diseases, metabolic disorders and inflammatory diseases.

In April 2008, Regulus Therapeutics entered into a worldwide strategic alliance with GlaxoSmithKline, or GSK, to discover, develop and market novel microRNA-targeted therapeutics to treat inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. In connection with this alliance, Regulus Therapeutics received $20.0 million in upfront payments from GSK, including a $15.0 million option fee and a loan of $5.0 million evidenced by a promissory note (guaranteed by Isis and us) that will convert into Regulus Therapeutics common stock under certain specified circumstances. Regulus Therapeutics could be eligible to receive development, regulatory and sales milestone payments for each of the four microRNA-targeted therapeutics discovered and developed as part of the alliance, and would also receive royalty payments on worldwide sales of products resulting from the alliance.

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. The issued patents and pending patent applications in the United States and in key markets around the world that we own or license claim fundamental features of siRNAs and RNAi therapeutics, as well as various chemical modifications and 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 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.

We believe that no other company possesses a portfolio of such broad and exclusive rights to the fundamental RNAi patents and patent applications required for the development and commercialization of RNAi therapeutics. 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 technology, as most recently evidenced by our new agreements with Tekmira and Protiva and our acquisition of the intellectual

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property in the emerging biological field of RNAa.

Our expertise in RNAi therapeutics and the strength of our broad intellectual property estate have enabled us to enter into alliances with leading companies, including Roche, Takeda, Novartis, Medtronic, Kyowa Hakko and Biogen Idec, as well as 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 any challenges that have arisen or may arise in this area.

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, 2007, which we filed with the Securities and Exchange Commission on March 10, 2008.

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,	
	2008	2007	2008	2007
Net revenues from research collaborators	$25,734	$ 16,315	$ 71,759	$ 32,665
Operating expenses	28,968	67,653	91,781	122,950
Loss from operations	(3,234)	(51,338)	(20,022)	(90,285)
Net loss	$ (2,858)	$(52,792)	$(16,857)	$ (87,128)

Revenues

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2008	2007	2008	2007
Roche	$ 13,671	$ 6,385	$ 40,447	$ 6,385
Takeda	5,357		7,431	
Government contract	3,129	2,383	12,091	6,600
Novartis	2,637	2,891	9,061	11,416
Other research collaborator	230	4,286	698	7,121
InterfeRx program, research reagent licenses and other	710	370	2,031	1,143
Total net revenues from research collaborators	$ 25,734	$ 16,315	$ 71,759	$ 32,665

Revenues increased significantly for the three months ended September 30, 2008 as compared to the three months ended September 30, 2007 primarily as a result of our August 2007 alliance with Roche, as well as our May 2008 alliance with Takeda. We received upfront payments totaling $331.0 million under the Roche alliance, of which $51.3 million was allocated to the purchase of 1,975,000 of our shares issued under the common stock purchase agreement and $278.2 million is being recognized as revenue on a straight-line basis over five years. In connection with the sale of the Alnylam Europe shares, Roche Kulmbach employees performed certain transition services for us at various levels through August 2008. We reimbursed Roche for these services at an agreed-upon rate. We recorded as contra revenue (a reduction of revenues) $0.2 million and $1.0 million for these services during the three and nine months ended September 30, 2008, respectively.

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In addition, in June 2008, we received upfront cash payments totaling $100.0 million under the Takeda alliance and, in October 2008, we received the first technology transfer milestone payment of $20.0 million. Takeda is required to make an additional $30.0 million in near-term payments to us upon achievement of specified technology transfer milestones. The $150.0 million in upfront and technology transfer milestone payments made or due to us under the Takeda alliance are being recognized as revenue on a straight-line basis over seven years.

For the three and nine months ended September 30, 2008 as compared to the three and nine months ended September 30, 2007, government contract revenues increased primarily as a result of our collaboration with DTRA, which began in the third quarter of 2007.

The decrease in Novartis revenues in the three and nine months ended September 30, 2008 as compared to the three and nine months ended September 30, 2007 was due primarily to a reduction in the number of resources allocated to the broad Novartis alliance.

Other research collaborator revenues decreased in the three and nine months ended September 30, 2008 as compared to the three and nine months ended September 30, 2007 due primarily to our termination of the Merck collaboration agreement in September 2007. We were recognizing the remaining deferred revenue under the Merck agreement on a straight-line basis over the remaining period of expected performance of four years. As a result of the termination, we recognized an aggregate of $3.5 million during the third quarter of 2007, which represented all of the remaining deferred revenue under the Merck agreement. In addition, during the three and nine months ended September 30, 2008, we reduced the number of resources allocated to, and received lower external expense reimbursement under, our collaboration with Biogen Idec. The pace and scope of future development under this collaboration is the responsibility of Biogen Idec. We expect limited resources to be expended on this program for the remainder of 2008.

Total deferred revenue of $349.5 million at September 30, 2008 consists of payments received from collaborators, primarily Roche, Takeda and Kyowa Hakko, that we have yet to recognize pursuant to our revenue recognition policies.

For the foreseeable future, we expect our revenues to continue to be derived primarily from our alliances with Roche, Takeda and Novartis, as well as other strategic alliances, collaborations, government contracts 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, 2008	% of Total Operating Expenses	Three Months Ended September 30, 2007	% of Total Operating Expenses	(Decrease) $	(Decrease) %
Research and development	$ 22,105	76%	$ 59,575	88%	$ (37,470)	(63%)
General and administrative	6,863	24%	8,078	12%	(1,215)	(15%)
Total operating expenses	$ 28,968	100%	$ 67,653	100%	$ (38,685)	(57%)

	Nine Months Ended	Nine Months Ended

	September 30, 2008	% of Total Operating Expenses	September 30, 2007	% of Total Operating Expenses	Increase (Decrease) $	Increase (Decrease) %
Research and development	$ 71,940	78%	$ 105,059	85%	$ (33,119)	(32%)
General and administrative	19,841	22%	17,891	15%	1,950	11%
Total operating expenses	$ 91,781	100%	$ 122,950	100%	$ (31,169)	(25%)

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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, 2008	% of Expense Category	Three Months Ended September 30, 2007	% of Expense Category	Increase (Decrease) $	Increase (Decrease) %
Research and development						
External services	$ 6,124	28%	$ 6,331	11%	$ (207)	(3%)
Compensation and related	4,264	19%	3,475	6%	789	23%
Clinical trial and manufacturing	3,113	14%	6,729	11%	(3,616)	(54%)
Non-cash stock-based compensation	2,908	13%	5,667	10%	(2,759)	(49%)
Facilities-related	2,768	13%	1,831	3%	937	51%
Lab supplies and materials	1,999	9%	1,482	2%	517	35%
License fees	361	2%	33,520	56%	(33,159)	(99%)
Other	568	2%	540	1%	28	5%
Total research and development expenses	$ 22,105	100%	$ 59,575	100%	$ (37,470)	(63%)

Research and development expenses decreased significantly during the three months ended September 30, 2008 as compared to the three months ended September 30, 2007 due primarily to higher license fees during the prior period consisting of $27.5 million in payments to certain entities, primarily Isis, as a result of our alliance with Roche and $6.0 million in payments for drug delivery-related activities. In addition, clinical trial and manufacturing expenses decreased during the three months ended September 30, 2008 as compared to the three months ended September 30, 2007 as a result of higher clinical trial and manufacturing expenses in the prior period in support of our clinical program for RSV, for which we began Phase II trials in June 2007.

Non-cash stock-based compensation expenses decreased significantly in the three months ended September 30, 2008 as compared to the three months ended September 30, 2007 due primarily to one time charges of $2.9 million from restricted stock grants and stock option modifications in August 2007 relating to the transfer of our former German employees to Roche Kulmbach as part of our alliance with Roche.

Partially offsetting these decreases, compensation and related expenses, lab supplies and materials, and facilities-related expenses increased during the three months ended September 30, 2008 as compared to the three months ended September 30, 2007 due to additional research and development headcount to support our alliances and expanding product pipeline.

We expect to continue to devote a substantial portion of our resources to research and development expenses and we expect that research and development expenses will remain consistent or increase slightly for the remainder of 2008 as we continue development of our and our collaborators product candidates and focus on drug delivery-related technologies.

	Nine Months	Nine Months

	Ended September 30, 2008	% of Expense Category	Ended September 30, 2007	% of Expense Category	Increase (Decrease) $	Increase (Decrease) %
Research and development						
External services	$ 18,541	26%	$ 14,410	14%	$ 4,131	29%
Compensation and related	12,511	17%	10,087	10%	2,424	24%
Clinical trial and manufacturing	10,148	14%	18,153	17%	(8,005)	(44%)
Non-cash stock-based compensation	8,079	11%	7,687	7%	392	5%
License fees	7,812	11%	42,156	40%	(34,344)	(81%)
Facilities-related	7,277	10%	6,035	6%	1,242	21%
Lab supplies and materials	5,848	8%	4,885	5%	963	20%
Other	1,724	3%	1,646	1%	78	5%
Total research and development expenses	$ 71,940	100%	$ 105,059	100%	$ (33,119)	(32%)

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Research and development expenses decreased during the nine months ended September 30, 2008 as compared to the nine months ended September 30, 2007 due primarily to higher license fees during the prior period consisting of $27.5 million in payments to certain entities, primarily Isis, as a result of our alliance with Roche, a non-cash license fee of $7.9 million and a cash license fee of $0.4 million related to the issuance of our stock to Tekmira during the first quarter of 2007 in connection with our original license agreement with Tekmira, and $6.0 million in payments for drug delivery-related activities. Partially offsetting this decrease was $5.0 million in payments made in June 2008 to certain entities, primarily Isis, as a result of the Takeda alliance, as well as a charge of $2.1 million in connection with our new Tekmira license agreement in May 2008.

Clinical trial and manufacturing expenses decreased during the nine months ended September 30, 2008 as compared to the nine months ended September 30, 2007 as a result of higher clinical trial and manufacturing expenses in the prior period in support of our clinical program for RSV, for which we began Phase II trials in June 2007.

Partially offsetting these decreases, external services expenses increased during the nine months ended September 30, 2008 as compared to the nine months ended September 30, 2007 as a result of higher expenses related to our government programs, our RSV program and our pre-clinical programs for the treatment of Huntington s disease and liver cancer, as well as higher expenses associated with our drug delivery-related collaborations. In addition, compensation and related, lab supplies and materials, and facilities-related expenses increased during the nine months ended September 30, 2008 as compared to the prior period due to additional research and development headcount to support our alliances and expanding product pipeline.

We do not track actual costs for most of our research and development programs or our personnel and personnel-related costs on a project-by-project basis because all of our programs are in the early stages of development. In addition, a significant portion of our research and development costs are not tracked by project as they benefit multiple projects or our technology platform. However, our collaboration agreements contain cost-sharing arrangements whereby certain costs incurred under the project are reimbursed. Costs reimbursed under the agreements typically include certain direct external costs and a negotiated full-time equivalent labor rate for the actual time worked on the project. In addition, we are reimbursed under our government contracts for certain allowable costs including direct internal and external costs. As a result, although a significant portion of our research and development expenses are not tracked on a project-by-project basis, we do track direct external costs attributable to, and the actual time our employees worked on, our collaborations and government contracts.

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, 2008	% of Expense Category	Three Months Ended September 30, 2007	% of Expense Category	Increase (Decrease) $	Increase (Decrease) %
General and administrative						
Consulting and professional services	$ 2,541	37%	$ 2,931	36%	$ (390)	(13%)
Non-cash stock-based compensation	1,741	25%	2,255	28%	(514)	(23%)
Compensation and related	1,384	20%	1,279	16%	105	8%
Facilities-related	504	7%	845	11%	(341)	(40%)
Insurance	186	3%	168	2%	18	11%
Other	507	8%	600	7%	(93)	(16%)

Total general and administrative expenses	$ 6, 863	100%	$ 8,078	100%	$ (1,215)	(15%)

The decrease in general and administrative expenses during the three months ended September 30, 2008 as compared to the three months ended September 30, 2007 was due primarily to our August 2007 alliance with Roche, which resulted in higher one-time non-cash stock-based compensation expenses of $0.9 million from restricted stock grants and stock option modifications relating to the transfer of our former German employees to Roche Kulmbach, as well as higher professional service fees during the prior period

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for business development activities, including work related to our alliance with Roche, our joint venture with Isis, Regulus Therapeutics, and the amendment and restatement of our Medtronic agreement.

	Nine Months Ended September 30, 2008	% of Expense Category	Nine Months Ended September 30, 2007	% of Expense Category	Increase (Decrease) $	Increase (Decrease) %
General and administrative						
Consulting and professional services	$ 6,717	34%	$ 6,472	36%	$ 245	4%
Non-cash stock-based compensation	4,938	25%	4,181	23%	757	18%
Compensation and related	4,279	22%	3,367	19%	912	27%
Facilities-related	1,853	9%	1,870	10%	(17)	(1%)
Insurance	505	3%	496	3%	9	2%
Other	1,549	7%	1,505	9%	44	3%
Total general and administrative expenses	$ 19,841	100%	$ 17,891	100%	$ 1,950	11%

The increase in general and administrative expenses during the nine months ended September 30, 2008 as compared to the nine months ended September 30, 2007 was due primarily to an increase in general and administrative headcount over the past year to support our growth and higher non-cash stock-based compensation.

Other income (expense)

We incurred $2.2 million and $5.4 million equity in loss of joint venture for the three and nine months ended September 30, 2008, respectively, as compared to $0.1 million for each of the three and nine months ended September 30, 2007, in each period related to our share of the net losses incurred by Regulus Therapeutics, which was formed in September 2007. In addition, during the three months ended September 30, 2008, we recorded an impairment charge of $1.6 million related to our May 2008 investment in Tekmira, as the decrease in the fair value of this investment was deemed to be other than temporary.

Interest income was $3.5 million and $11.7 million for the three and nine months ended September 30, 2008, respectively, as compared to $4.3 million and $9.6 million for the three and nine months ended September 30, 2007, respectively. The decrease during the three months ended September 30, 2008 as compared to the three months ended September 30, 2007 was due to lower average interest rates, partially offset by higher average cash, cash equivalent and marketable securities balances resulting primarily from the $331.0 million in proceeds we received in August 2007 from our alliance with Roche and the $100.0 million in proceeds we received in June 2008 from our alliance with Takeda. The increase during the nine months ended September 30, 2008 as compared to the nine months ended September 30, 2007 was due to our higher average cash, cash equivalent and marketable securities balances, partially offset by lower average interest rates during the nine months ended September 30, 2008.

Interest expense was $0.2 million and $0.6 million for the three and nine months ended September 30, 2008, respectively, as compared to $0.3 million and $0.8 million for the three and nine months ended September 30, 2007, respectively. Interest expense in each period was related to borrowings under our lines of credit used to finance capital equipment purchases.

Income tax expense, primarily as a result of our 2007 alliance with Roche, was a benefit from income taxes of $0.8 million and a provision for income taxes of $0.7 million for the three and nine months ended September 30, 2008, respectively, as compared to a provision for income taxes of $5.2 million for each of the three and nine months

ended September 30, 2007. During the third quarter of 2008, in review of our calculation of estimated state income tax expense for 2008, we discovered that we had overstated our state income tax provision for 2008 and therefore, our state income taxes will be less than originally anticipated. To correct the state income tax provision, we recorded a credit to income taxes of $0.9 million in the three months ended September 30, 2008, resulting in a net income tax benefit of $0.8 million for the three months ended September 30, 2008 and a tax provision of $0.7 million for the nine months ended September 30, 2008. Income tax expense of $5.2 million for the three and nine months ended September 30, 2007 was a result of the proceeds from the sale of our German operations to Roche in connection with our alliance with Roche.

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Liquidity and Capital Resources

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

	Nine Months Ended September 30,	
	2008	2007
Net loss	$ (16,857)	$ (87,128)
Adjustments to reconcile net loss to net cash used in operating activities	24,230	25,189
Changes in operating assets and liabilities	62,967	266,896
Net cash provided by operating activities	70,340	204,957
Net cash provided by (used in) investing activities	14,537	(189,737)
Net cash provided by financing activities	6,639	57,880
Effect of exchange rate on cash	64	(508)
Net increase in cash and cash equivalents	91,580	72,592
Cash and cash equivalents, beginning of period	105,157	127,955
Cash and cash equivalents, end of period	$ 196,737	$ 200,547

Since we commenced operations in 2002, we have generated significant losses. As of September 30, 2008, we had an accumulated deficit of $242.9 million. As of September 30, 2008, we had cash, cash equivalents and marketable securities of $520.2 million, compared to cash, cash equivalents and marketable securities of $455.6 million as of December 31, 2007. We invest primarily in cash equivalents, U.S. government obligations, high-grade corporate notes 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 significant impairment charges to our fixed income marketable securities as of September 30, 2008.

Operating activities

We have required significant amounts of cash to fund our operating activities as a result of net losses since our inception. The decrease in net cash provided by operating activities for the nine months ended September 30, 2008 as compared to the nine months ended September 30, 2007 was due primarily to the proceeds received from our August 2007 Roche alliance partially offset by the proceeds received from our May 2008 alliance with Takeda. Offsetting the proceeds from the Takeda alliance, the main components of our use of cash in operating activities for the nine months ended September 30, 2008 consisted of the net loss and changes in our working capital. Cash used in operating activities is adjusted for non-cash items to reconcile net loss to net cash provided by or used in operating activities. These non-cash adjustments consist primarily of stock-based compensation, equity in loss of joint venture and depreciation and amortization. We had an increase in deferred revenue of $86.2 million for the nine months ended September 30, 2008 as compared to the nine months ended September 30, 2007 due primarily to the proceeds received from our Takeda and Kyowa Hakko alliances. Additionally, accrued expenses and other decreased $3.0 million for the nine months ended September 30, 2008.

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, 2008, net cash provided by investing activities of $14.5 million resulted primarily from net sales and maturities of marketable securities of $24.1 million. Also included in our

investing activities for the nine months ended September 30, 2008 were purchases of property and equipment of $9.5 million related to the expansion of our Cambridge facility. For the nine months ended September 30, 2007, net cash used in investing activities of $189.7 million resulted primarily from net purchases of marketable securities of $178.5 million.

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Financing activities

For the nine months ended September 30, 2008, net cash provided by financing activities was $6.6 million as compared to $57.9 million provided by financing activities for the nine months ended September 30, 2007. For the nine months ended September 30, 2008, net cash provided by financing activities was due primarily to proceeds of $5.4 million from our issuance of shares to Novartis in May 2008. Net cash provided by financing activities for the nine months ended September 30, 2007 consisted primarily of proceeds of $42.5 million from our sale of 1,975,000 shares of our common stock to Roche in connection with the establishment of the Roche alliance.

In March 2006, we entered into an agreement with Oxford Finance Corporation, or Oxford, to establish an equipment line of credit for up to $7.0 million to help support capital expansion of our facility in Cambridge, Massachusetts and capital equipment purchases. During 2006, we borrowed an aggregate of $4.2 million from Oxford pursuant to the agreement. In May 2007, we borrowed an aggregate of $1.0 million from Oxford pursuant to the agreement. These amounts are being repaid in 36 to 48 monthly installments. As of December 31, 2007, we were no longer able to draw down funds under the Oxford line of credit.

In March 2004, we entered into an equipment line of credit with Lighthouse Capital Partners V, L.P., or Lighthouse, to finance leasehold improvements and equipment purchases of up to $10.0 million. All draw-downs began to be repaid over 48 months beginning September 30, 2005. On the maturity of each equipment advance under the line of credit, we are required to pay, in addition to the principal and interest due, an additional amount of 11.5% of the original principal. This amount is being accrued over the applicable borrowing period as additional interest expense.

As of September 30, 2008, we had an aggregate outstanding balance of $3.9 million under our loan agreements.

During the current downturn in global financial markets, some companies have experienced difficulties accessing their cash equivalents, investment securities and raising capital generally, which have had a material adverse impact on their liquidity. Based on our current operating plan, we believe that our existing cash position, for which we have not recognized any significant impairment charges, together with the cash we expect to generate under our current alliances, including our Novartis, Roche and Takeda alliances, will be sufficient to fund our planned operations for at least the next several years, during which time we expect to further the development of our product candidates, conduct clinical trials, extend the capabilities of our technology platform and continue to prosecute patent applications and otherwise build and maintain our patent portfolio. However, we may require significant additional funds earlier than we currently expect in order to develop, commence clinical trials for and commercialize any product candidates.

In the longer term, we may seek additional funding through additional collaborative arrangements and public or private financings. Additional funding 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, further dilution to our existing stockholders may result. If we are unable to obtain funding on a timely basis, we may be required to significantly 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 drug 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;

the timing, receipt and amount of funding under current and future government contracts, if any;

our ability to maintain and establish additional collaborative arrangements;

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the resources, time and costs required to successfully initiate and complete our pre-clinical and clinical trials, obtain regulatory approvals, protect our intellectual property and obtain and maintain licenses to third-party intellectual property;

the cost of preparing, filing, prosecuting, maintaining and enforcing patent claims;

progress in the research and development programs of Regulus Therapeutics; 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, 2007. In addition, in May 2008, in connection with Tekmira s acquisition of Protiva and our purchase of $5.0 million of Tekmira s common stock, we and Tekmira cancelled our $5.0 million capital equipment loan to Tekmira, which Tekmira never drew down.

Recent Accounting Pronouncements

In December 2007, the Financial Accounting Standards Board, or FASB, reached a consensus on EITF No. 07-1, Accounting for Collaborative Arrangements, or EITF 07-1. EITF 07-1 requires collaborators to present the results of activities for which they act as the principal on a gross basis and report any payments received from (made to) other collaborators based on other applicable GAAP or, in the absence of other applicable GAAP, based on analogy to authoritative accounting literature or a reasonable, rational and consistently applied accounting policy election. Further, EITF 07-1 clarifies that the determination of whether transactions within a collaborative arrangement are part of a vendor-customer (or analogous) relationship subject to EITF Issue No. 01-9, Accounting for Consideration Given by a Vendor to a Customer (Including a Reseller of the Vendor s Products). EITF 07-1 will be effective beginning on January 1, 2009. We are evaluating the potential impact of EITF 07-1 on our consolidated financial statements.

In December 2007, the FASB issued Statement of Financial Accounting Standards, or SFAS, No. 141R, Business Combinations, or SFAS 141R. SFAS 141R establishes principles and requirements for how an acquirer recognizes and measures in its financial statements the identifiable assets acquired, the liabilities assumed, any noncontrolling interest in the acquiree and the goodwill acquired. SFAS 141R also establishes disclosure requirements to enable the evaluation of the nature and financial effects of the business combination. SFAS 141R is effective for fiscal years beginning after December 15, 2008. We are evaluating the potential impact of SFAS 141R on our consolidated financial statements.

In December 2007, the FASB issued SFAS No. 160, Noncontrolling Interests in Consolidated Financial Statements, an amendment of ARB No. 51, or SFAS 160. SFAS 160 changes the accounting for and reporting of noncontrolling or minority interests (now called noncontrolling interests) in consolidated financial statements. SFAS 160 is effective January 1, 2009. When implemented, prior periods will be recast for the changes required by SFAS 160. We do not anticipate the adoption of SFAS 160 will have a material impact on our consolidated financial statements.

In May 2008, the FASB issued SFAS No. 162, The Hierarchy of Generally Accepted Accounting Principles, or SFAS 162. SFAS 162 identifies the sources of accounting principles and the framework for selecting the principles used (order of authority) in the preparation of financial statements that are presented in conformity with generally accepted accounting standards in the United States. SFAS 162 is effective 60 days following the SEC s approval of the Public Company Accounting Oversight Board amendments to AU Section 411, The Meaning of Present Fairly in Conformity with Generally Accepted Accounting Principles. We do not anticipate the adoption of SFAS 162 will have a material impact on our consolidated financial statements.

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 obligations, high-grade corporate notes 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

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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. A 10% decrease in market interest rates at September 30, 2008 would impact the net fair value of such interest-sensitive financial instruments by $2.1 million. 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 significant impairment charges to our fixed income marketable securities as of September 30, 2008.

ITEM 4. CONTROLS AND PROCEDURES

Our management, with the participation of our chief executive officer and vice president of finance and treasurer, evaluated the effectiveness of our disclosure controls and procedures as of September 30, 2008. The term disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, 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, 2008, 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(d) and 15d 15(d) under the Exchange Act) occurred during the three months ended September 30, 2008 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

PART II. OTHER INFORMATION

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. 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 undertake no obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise. 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 an Early Stage Company

Because we have a short operating history, there is a limited amount of information about us upon which you can evaluate our business and prospects.

Our operations began in 2002 and we have only a limited operating history upon which you can evaluate our business and prospects. In addition, as an early-stage company, 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

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relevant cell tissue;
build and maintain a strong intellectual property portfolio;

gain acceptance for the development of our product candidates and 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.

Relatively few drug 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. If we do not successfully develop and commercialize drugs based upon our technological approach, we may not become profitable and the value of our common stock will decline.

Further, our focus solely on RNAi technology for developing drugs, as opposed to multiple, more proven technologies for drug development, increases the risks associated with the ownership of our common stock. If we are not successful in developing 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 be profitable.

We have experienced significant operating losses since our inception. As of September 30, 2008, we had an accumulated deficit of $242.9 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 such 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 revenue we generate over the next several years will be from alliances with pharmaceutical companies or funding from contracts with the government, but cannot be certain that we will be able to secure or maintain these alliances or contracts, or meet the obligations or achieve any milestones that we may be required to meet or achieve to receive payments.

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

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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, diversify our product offerings 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 any product candidates, and to manufacture and market any products that are approved for commercial sale. Because the successful development of our products is uncertain, 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 drug 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;
- the timing, receipt and amount of funding under current and future government contracts, if any;
- our ability to maintain and establish additional collaborative arrangements;
- the resources, time and costs required to initiate and complete our pre-clinical and clinical trials, obtain regulatory approvals, protect our intellectual property and obtain and maintain licenses to third-party intellectual property;
- the cost of preparing, filing, prosecuting, maintaining and enforcing patent claims;
- progress in the research and development programs of Regulus Therapeutics; and
- the timing, receipt and amount of sales and royalties, if any, from our potential products.

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

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, further dilution to our stockholders will result. In addition, our investor rights agreement with Novartis provides Novartis with the right generally to maintain its ownership percentage in us and our common stock purchase agreement with Roche contains a similar provision. In May 2008, Novartis purchased 213,888 shares of our common stock at a purchase price of $25.29 per share. The purchase by Novartis of these shares in May 2008 resulted in a 0.5% increase in Novartis ownership position to 13.4%. At September 30, 2008, Novartis ownership position was 13.2%. While the exercise of these rights by Novartis provided us with $5.4 million in cash, and the exercise in the future by Novartis or Roche may provide us with additional funding under some circumstances, this exercise and any future exercise of these rights by Novartis or Roche 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. If we are unable to obtain funding on a timely basis, we may be required to

significantly 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, 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 consolidated financial statements prove inaccurate, our actual results may vary from those reflected in our projections and accruals.

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Our consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States. The preparation of these 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 balance and our investments in marketable debt securities are subject to risks which may cause losses and affect the liquidity of these investments.

At September 30, 2008, we had $520.2 million in cash, cash equivalents and marketable securities. We historically have invested these amounts in corporate bonds, commercial paper, securities issued 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, which may be affected by U.S. sub-prime mortgage defaults that have affected various sectors of the financial markets and caused credit and liquidity issues. 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 consolidated financial statements. In addition, should our investments cease paying or reduce the amount of interest paid to us, our interest income would suffer. These market risks associated with our investment portfolio may have a negative adverse effect on our results of operations, liquidity and financial condition.

Risks Related to Our Dependence on Third Parties

Our collaboration with Novartis is important to our business. If this collaboration is unsuccessful, Novartis terminates this collaboration or this collaboration results in competition between us and Novartis for the development of drugs targeting the same diseases, our business could be adversely affected.

In October 2005, we entered into a collaboration agreement with Novartis. Under this agreement, Novartis can select a defined but limited number of disease targets on an exclusive basis towards which the parties will collaborate to develop drug candidates. Novartis pays a portion of the costs to develop these drug candidates and will commercialize and market any products derived from this collaboration. In addition, Novartis pays us certain pre-determined amounts based on the achievement of pre-clinical and clinical milestones as well as royalties on the annual net sales of any products derived from this collaboration. The Novartis agreement has an initial term of three years, with the option for two additional one-year extensions at the election of Novartis. In July 2008, Novartis elected to extend the initial term for an additional year, through October 2009. Novartis retains the right to extend the term for a second additional year, which right must be exercised no later than July 2009. Novartis may elect to terminate this collaboration in the event of a material uncured breach by us. We expect that a substantial amount of funding will come from this collaboration. If this collaboration is unsuccessful, or if it is terminated, our business could be adversely affected.

This agreement also provides Novartis with a non-exclusive option to a broad platform license to integrate our intellectual property into Novartis operations and develop products without our involvement for a pre-determined fee, which option may be exercised during the term of our collaboration. If Novartis elects to exercise this option, Novartis could become a competitor of ours in the development of RNAi-based drugs targeting the same diseases. Novartis has significantly greater financial resources and far more experience than we do in developing and marketing drugs, which could put us at a competitive disadvantage if we were to compete with Novartis in the development of RNAi-based drugs targeting the same disease. Accordingly, the exercise by Novartis of this option could adversely affect our business.

Our agreement with Novartis allows us to continue to develop products on an exclusive basis on our own with respect to targets not selected by Novartis for inclusion in the collaboration. We may need to form additional alliances to develop products. However, our agreement with Novartis provides Novartis with a right of first offer, for a defined term, in the event that we propose to enter into an agreement with a third party with respect to such targets. This right of first offer may make it difficult for us to form future alliances around specific targets with other parties.

Our license and collaboration agreement with Roche is important to our business. If Roche does not successfully develop drugs pursuant to this agreement or it results in competition between us and Roche for the development of

drugs targeting the same diseases, our business could be adversely affected.

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In July 2007, we and, for limited purposes, Alnylam Europe, 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 as well as our collaboration agreements. The license is limited to the therapeutic areas of oncology, respiratory diseases, metabolic diseases and certain liver diseases and may be expanded to include other therapeutic areas under certain circumstances. As such, Roche could become a competitor of ours in the development of RNAi-based drugs targeting the same diseases. Roche has significantly greater financial resources than we do and has far more experience in developing and marketing drugs, which could put us at a competitive disadvantage if we were to compete with Roche in the development of RNAi-based drugs targeting the same disease. Roche is required to make payments to us upon achievement of specified development and sales milestones set forth in the license and collaboration agreement and royalty payments based on worldwide annual net sales, if any, of RNAi therapeutic products by Roche, its affiliates and sublicensees. If Roche fails to successfully develop products using this technology, we may not receive any such milestone or royalty payments.

Our license and collaboration agreement with Takeda is important to our business. If Takeda does not successfully develop drugs pursuant to this agreement or it results in competition between us and Takeda for the development of drugs targeting the same diseases, our business could be adversely affected.

In May 2008, we entered into a license and collaboration agreement with Takeda. Under the license and collaboration agreement we granted Takeda 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 as well as our collaboration agreements. The license is limited to the therapeutic areas of oncology and metabolic diseases, which may be expanded to include other therapeutic areas under certain circumstances. As such, Takeda could become a competitor of ours in the development of RNAi-based drugs targeting the same diseases. Takeda has significantly greater financial resources than we do and has far more experience in developing and marketing drugs, which could put us at a competitive disadvantage if we were to compete with Takeda in the development of RNAi-based drugs targeting the same disease. Takeda is required to make payments to us upon achievement of specified development and sales milestones set forth in the license and collaboration agreement and royalty payments based on worldwide annual net sales, if any, of RNAi therapeutic products by Takeda, its affiliates and sublicensees. In addition, we have agreed that for a period of five years, we will not grant any other party rights to develop RNAi therapeutics in the Asian territory. If Takeda fails to successfully develop products using this technology, we may not receive any milestone or royalty payments under the agreement and for a period of five years will be limited in our ability to form alliances with other parties in the Asian territory. In addition, we have the option, exercisable until the start of Phase III development, to opt-in under a 50-50 profit sharing agreement to the development and commercialization in the United States of up to four Takeda licensed products, and would be entitled to opt-in rights for two additional products for each additional field expansion, if any, elected by Takeda under the collaboration agreement. If Takeda fails to successfully develop products, we may not realize any economic benefit from these opt-in rights.

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 drug candidates. If we are unsuccessful in forming or maintaining these alliances on favorable terms, our business may not succeed.

We do not have any capability for sales, marketing or distribution and have limited capabilities for drug development. In addition, we believe that other companies are expending substantial resources in developing safe and effective means of delivering siRNAs to relevant cell and tissue types. Accordingly, we have entered into alliances with other companies that we believe can provide such capabilities, including, for example, Medtronic and Kyowa Hakko, and we intend to enter into additional alliances in the future. For example, we intend to enter into (1) non-exclusive platform alliances which will enable our collaborators to develop RNAi therapeutics and will bring in additional funding with which we can develop our RNAi therapeutics, and (2) alliances to jointly develop specific drug candidates and to jointly commercialize RNAi therapeutics, if they are approved, and/or ex-U.S. market geographic partnerships on specific RNAi therapeutic programs. In such alliances, we may expect our collaborators to provide

substantial capabilities in delivery of RNAi therapeutics to the relevant cell or tissue type, clinical development, regulatory affairs, and/or marketing and sales. For example, under our collaboration with Medtronic, we are jointly developing ALN-HTT, an RNAi therapeutic for Huntington s disease, which would be delivered using an implanted infusion device developed by Medtronic. The success of this collaboration will depend, in part, on Medtronic s expertise in the area of delivery by infusion device.

We may not be successful in entering into such alliances on favorable terms due to various factors, including Novartis right of first offer on our drug targets. Even if we do succeed in securing such alliances, we may not be able to maintain them if, for example, development or approval of a drug candidate is delayed or sales of an approved drug are disappointing. Furthermore, any delay in entering into collaboration agreements could delay the development and commercialization of our drug candidates and reduce their competitiveness even if they reach the market. Any such delay related to our collaborations could adversely affect our business.

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For certain drug 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 collaborations with Novartis, as well as collaborations with Medtronic, NIAID and DTRA. We may not, however, be able to enter into additional collaborations, 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 a particular drug candidate, we may not have sufficient funds to develop this or any other drug candidate internally, or to bring any drug candidates to market. If we do not have sufficient funds to develop and bring our drug candidates to market, we will not be able to generate sales revenues from these drug 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 drug 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. Our agreement with Kyowa Hakko for the development and commercialization of ALN-RSV01 for the treatment of RSV infection in Japan and other major markets in Asia may be terminated by Kyowa Hakko without cause upon 180-days prior written notice to us, subject to certain conditions. If a collaborator terminates its collaboration with us, for breach or otherwise, it would be difficult for us to attract new collaborators and could adversely affect how we are perceived in the business and financial communities. In addition, a collaborator, or in the event of a change in control of a collaborator, the successor entity, could determine that it is in its financial interest 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 drug 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 depend on government contracts to partially fund our research and development efforts and may enter into additional government contracts in the future. If current or future government funding, if any, is reduced or delayed, our drug development efforts for such funded programs would be negatively affected.

In September 2006, NIAID awarded us a contract for up to $23.0 million over four years to advance the development of a broad spectrum RNAi anti-viral therapeutic for hemorrhagic fever virus, including the Ebola virus. Of the $23.0 million, the government initially committed to pay us $14.2 million over the first two years of the contract and, in June 2008, as a result of the progress of the program, the government awarded us an additional $7.5 million through September 2009 for the third year of the contract. We cannot be certain that the government will appropriate the funds necessary for this contract in future budgets. In addition, the government can terminate the agreement in specified circumstances. If we do not receive the $23.0 million we expect to receive under this contract, we may not be able to develop therapeutics to treat Ebola.

In August 2007, DTRA awarded us a contract to advance the development of a broad spectrum RNAi anti-viral therapeutic for hemorrhagic fever virus infection. This federal contract could provide us with up to $38.6 million in funding through February 2011 to develop RNAi therapeutics for hemorrhagic fever virus infection. This contract is

with DTRA under its 2007 Medical Science and Technology Chemical and Biological Defense Transformational Medical Technologies Initiative, the mission of which is to provide state-of-the-art defense capabilities to United States military personnel by addressing traditional and non-traditional biological threats. Of the $38.6 million in funding, the government has committed to pay us up to $10.9 million through February 2009, which term includes a six-month extension granted by DTRA in July 2008. Subject to the progress of the program and budgetary considerations

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in future years, the remaining $27.7 million may be paid over the last two years of the contract. If we do not receive the $38.6 million we expect to receive under this contract, we may not be able to develop therapeutics to treat hemorrhagic fever virus infection.

Regulus Therapeutics, our joint venture with Isis, is important to our business. If Regulus Therapeutics does not successfully develop drugs pursuant to this license and collaboration agreement or Regulus Therapeutics is sold to Isis or a third-party, our business could be adversely affected.

In September 2007, we and Isis created Regulus Therapeutics to discover, develop and commercialize microRNA therapeutics. Formed as a joint venture, Regulus Therapeutics intends to address therapeutic opportunities that arise from abnormal expression or mutations in microRNAs. Generally, we do not have rights to pursue microRNA therapeutics independently of Regulus Therapeutics. If Regulus Therapeutics is unable to discover, develop and commercialize microRNA therapeutics, our business could be adversely affected.

In addition, subject to certain conditions, we and Isis each have the right to initiate a buy-out of Regulus Therapeutics assets, including Regulus Therapeutics intellectual property and rights to licensed intellectual property. The limited liability company agreement provides that following such initiation of a buy-out, we and Isis will mutually determine whether to sell Regulus Therapeutics to us, Isis or a third party. We may not have sufficient funds to buy out Isis interest in Regulus Therapeutics and we may not be able to obtain the financing to do so. In addition, Isis may not be willing to sell their interest in Regulus Therapeutics. If Regulus Therapeutics is sold to Isis or a third party, we may lose our rights to participate in the development and commercialization of microRNA therapeutics. If we and Isis are unable to negotiate a sale of Regulus Therapeutics, Regulus Therapeutics will distribute and assign its rights, interests and assets to us and Isis in accordance with our percentage interests, except for Regulus Therapeutics intellectual property and license rights, to which each of us and Isis will receive co-exclusive rights, subject to certain specified exceptions. In this event, we could face competition from Isis in the development of microRNA therapeutics.

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

We have very limited manufacturing experience. Our internal manufacturing capabilities are limited to small-scale production of non-good manufacturing practice material for use in *in vitro* and *in vivo* experiments. Our products utilize specialized formulations, such as liposomes, 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 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. 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. Only a limited number of manufacturers 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. In addition, to fulfill our siRNA requirements we may need to secure alternative suppliers of synthetic siRNAs. 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. 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 these manufacturers to properly formulate our siRNAs for delivery could also result in unusable product and cause delays in our discovery and development process, as well as additional expense to us.

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 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 enter into manufacturing arrangements with third parties, we will depend on these third parties to perform their obligations in a timely manner and consistent with regulatory requirements, including those related to quality control and quality assurance. The failure of a third-party manufacturer to perform its obligations as expected could adversely affect our business in a

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number of ways, including:

- we may not be able to initiate or continue clinical trials of products that are under development;
- we may be delayed in submitting regulatory applications, or receiving regulatory approvals, for our products candidates;
- we may lose the cooperation of our collaborators;
- 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 a 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 with reasonable terms, if at all. In some cases, the technical skills required to manufacture our product may be unique to the original manufacturer and we may have difficulty transferring such skills to a back-up nor 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. 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.

We have no sales, marketing or distribution experience and expect to depend significantly on third parties who may not successfully commercialize our products.

We have no sales, marketing or distribution experience. We expect to rely heavily on third parties to launch and market certain of our product candidates, if approved. We may have limited or no control over the 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 on Kyowa Hakko to commercialize ALN-RSV01 in Japan and other Asian territories under our license agreement with them. If Kyowa Hakko is not successful in its commercialization efforts, our future revenues may be adversely affected.

To develop internal sales, distribution and marketing capabilities, we will have to invest significant amounts of financial and management resources. For products where we decide to 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.

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.

Although we have generally been successful in our recruiting efforts, 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

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retain suitably qualified individuals, and our failure to do so could have an adverse effect on our ability to implement our business plan.

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

Since we commenced operations in 2002, we have grown substantially. As of September 30, 2008, we had approximately 157 employees in our facility in Cambridge, Massachusetts. Our rapid and substantial growth may place a strain on our administrative and operational infrastructure. If drug 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. As our operations expand, we expect that we will need to manage additional relationships with various collaborators, suppliers and other organizations. Our ability to manage our operations and growth will require us to continue to improve our operational, financial and management controls, reporting systems 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.

Risks Related to Our Industry

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

Any drug candidates we develop may fail in development or be delayed to a point where they do not become commercially viable.

Pre-clinical testing and clinical trials of new drug candidates are lengthy and expensive and the historical failure rate for drug candidates is high. We are developing our most advanced product candidate, ALN-RSV01, for the treatment of RSV infection. In January 2008, we completed a Phase II trial designed to evaluate the safety, tolerability and anti-viral activity of ALN-RSV01 in adult subjects experimentally infected with RSV. We commenced a second Phase II trial in April 2008 to assess the safety and tolerability of ALN-RSV01 in adult lung transplant patients naturally infected with RSV and we intend to continue the clinical development of ALN-RSV01. However, we may not be able to further advance this or any other product candidate through clinical trials. If we successfully enter into clinical studies, the results from pre-clinical testing or early clinical trials of a drug candidate may not predict the results that will be obtained in subsequent human clinical trials. We, the FDA or other applicable regulatory authorities, or an institutional review board, or IRB, may suspend clinical trials of a drug 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 drug 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 drug candidate for any or all indications of use.

Clinical trials of a new drug candidate require the enrollment of a sufficient number of patients, including patients who are suffering from the disease the drug 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 nature of the protocol, the proximity of patients to clinical sites, the availability of effective treatments for the relevant disease, the seasonality of infections and the eligibility criteria for the clinical trial. Delays in patient enrollment can result in increased costs and longer development times.

Clinical trials also require the review and oversight of IRBs, which approve and 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 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 drug 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 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 drug candidate that is affected, or development of any of our other drug candidates. We may also lose, or be unable to enter into, collaborative arrangements for the affected drug candidate and for other drug candidates we are developing.

Delays in clinical trials could reduce the commercial viability of our drug candidates. Any of the following could, among other things, delay our clinical trials:

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delays in filing initial drug applications;

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 trials or problems in obtaining or maintaining IRB approval of trials;

delays in enrolling patients and volunteers into 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 drug candidates similar to ours;

inadequate supply or quality of drug candidate materials or other materials necessary for the conduct of our clinical trials;

serious and unexpected drug-related side effects experienced by participants in our clinical trials or by individuals using drugs similar to our product candidates; or

unfavorable FDA or other regulatory agency inspection and review of a clinical trial site or records of any clinical or pre-clinical investigation.

Even if we successfully complete clinical trials of our drug candidates, any given drug candidate may not prove to be an effective treatment for the diseases for which it was being tested.

The FDA approval process may be delayed for any drugs we develop that require the use of specialized drug delivery devices.

Some drug candidates that we develop may need to be administered using specialized drug delivery devices that deliver RNAi therapeutics directly to diseased parts of the body. For example, we believe that product candidates we develop for Parkinson s disease, HD or other central nervous system diseases may need to be administered using such a device. For neurodegenerative diseases, we have entered into a collaboration agreement with Medtronic to pursue potential development of drug-device combinations incorporating RNAi therapeutics. We may not achieve successful development results under this collaboration and may need to seek other collaboration partners to develop alternative drug delivery systems, or utilize existing drug delivery systems, for the direct delivery of RNAi therapeutics for these diseases. While we expect to rely on drug delivery systems that have been approved by the FDA or other regulatory agencies to deliver drugs like ours to similar physiological sites, we, or our collaborator, may need to modify the design or labeling of such delivery device for some products we may develop. In such an event, the FDA may regulate the product as a combination product or require additional approvals or clearances for the modified delivery device. Further, to the extent the specialized delivery device is owned by another company, we would need that company s cooperation to implement the necessary changes to the device, or its labeling, and to obtain any additional approvals or clearances. In cases where we do not have an ongoing collaboration with the company that makes the device, obtaining such additional approvals or clearances and the cooperation of such other company could significantly delay and increase the cost of obtaining marketing approval, which could reduce the commercial viability of our drug candidate. In summary, we may be unable to find, or experience delays in finding, suitable drug delivery systems to administer RNAi therapeutics directly to diseased parts of the body, which could negatively affect our ability to successfully commercialize these RNAi therapeutics.

We may be unable to obtain United States or foreign regulatory approval and, as a result, be unable to commercialize our drug candidates.

Our drug candidates are subject to extensive governmental regulations relating to, among other things, research, testing, development, manufacturing, safety, efficacy, recordkeeping, labeling, 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 drug candidates we may develop will obtain the appropriate regulatory approvals necessary for us or our collaborators to begin selling them.

We have very 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 complexity of the drug candidate. Any analysis we perform of data from

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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. For example, the recently enacted Food and Drug Administration Amendments Act of 2007, or FDAAA, may make it more difficult and costly for us to obtain regulatory approval of our product candidates and to produce, market and distribute products after approval. The FDAAA grants a variety of new powers to the FDA, many of which are aimed at improving the safety of drug products before and after approval. In particular, it authorizes the FDA to, among other things, require post-approval studies and clinical trials, mandate changes to drug labeling to reflect new safety information, and require risk evaluation and mitigation strategies, or REMS, for certain drugs, including certain currently approved drugs. In addition, it significantly expands the federal government s clinical trial registry and results databank and creates new restrictions on the advertising and promotion of drug products. Under the FDAAA, companies that violate the new law are subject to substantial civil monetary penalties.

Because the drugs we are intending to develop may represent a new class of drug, the FDA has not yet established any definitive policies, practices or guidelines in relation to these drugs. While the product candidates that we are currently developing are regulated as a new drug under the Federal Food, Drug, and Cosmetic Act, the FDA could decide to regulate them or other products we may develop as biologics under the Public Health Service Act. 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 will 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 number of approvals to market new drugs has declined.

Any delay or failure in obtaining required approvals could have a material adverse effect on our ability to generate revenues from the particular drug candidate. Furthermore, any regulatory approval to market a product may be subject to limitations on the indicated uses for which we may market the product. These limitations may limit the size of the market for the product and affect reimbursement by third-party payors.

We are also subject to numerous foreign regulatory requirements governing, among other things, the conduct of clinical trials, manufacturing and marketing authorization, pricing and third-party reimbursement. The foreign regulatory approval process 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 assure approval by regulatory authorities outside the United States and vice versa.

If our pre-clinical testing does not produce successful results or our clinical trials do not demonstrate safety and efficacy in humans, we will not be able to commercialize our drug candidates.

Before obtaining regulatory approval for the sale of our drug 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 drug 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. Success in pre-clinical testing and early clinical trials does not ensure that later clinical trials will be successful, and interim results of a clinical trial do not necessarily predict final results.

A failure of one of 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 our ability to receive regulatory approval or commercialize our drug candidates, including:

- regulators or IRBs may not authorize us to commence or continue a clinical trial or conduct a clinical trial at a prospective trial site;

- 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;

enrollment in our clinical trials may be slower than we anticipate or participants may drop out of our clinical trials at a higher

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rate than we anticipate, resulting in significant delays;

our third party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner;

we might have to suspend or terminate our clinical trials if the participants are being exposed to unacceptable health risks;

IRBs or regulators, including the FDA, may require that we hold, suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements;

the cost of our clinical trials may be greater than we anticipate;

the supply or quality of our drug candidates or other materials necessary to conduct our clinical trials may be insufficient or inadequate;

effects of our drug candidates may not be the desired effects or may include undesirable side effects or the drug candidates may have other unexpected characteristics; and

effects of our drug candidates may not be clear, or we may disagree with regulatory authorities, including the FDA, about how to interpret the data generated in our clinical trials.

Even if we obtain regulatory approvals, our marketed drugs will be subject to ongoing regulatory review. If we fail to comply with continuing United States and foreign regulations, we could lose our approvals to market drugs 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 vigilance required as a condition of approval. The manufacturer and manufacturing facilities we use to make any of our drug candidates will also be subject to periodic review and inspection by the FDA. The discovery of any new or previously unknown problems with the product, manufacturer or facility may result in restrictions on the drug or manufacturer or facility, including withdrawal of the drug from the market. We do not have, and currently do not intend to develop, the ability to manufacture material for our clinical trials or on a commercial scale. 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. Our product promotion and advertising is also subject to regulatory requirements and continuing regulatory review.

If we fail to comply with applicable continuing regulatory requirements, we may be subject to fines, suspension or withdrawal of regulatory approval, product recalls and seizures, operating restrictions 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, efficacy and ease of administration of our product candidates;

the willingness of patients to accept potentially new routes of administration;

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the success of our physician education programs;

the availability of 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.

Even if we develop RNAi therapeutic products for the prevention or treatment of infection by hemorrhagic fever viruses such as Ebola and/or pandemic flu virus, governments may not elect to purchase such products, which could adversely affect our business.

We expect that governments will be the only purchasers of any products we may develop for the prevention or treatment of hemorrhagic fever viruses such as Ebola or pandemic flu. In the future, we may also initiate additional programs for the development of product candidates for which governments may be the only or primary purchasers. However, governments will not be required to purchase any such products from us and may elect not to do so, which could adversely affect our business. For example, although the focus of our Ebola program is to develop RNAi therapeutic targeting gene sequences that are highly conserved across known Ebola viruses, if the sequence of any Ebola virus that emerges is not sufficiently similar to those we are targeting, any product candidate that we develop may not be effective against that virus. Accordingly, while we expect that any RNAi therapeutic we develop for the treatment of Ebola could be stockpiled by governments as part of their biodefense preparations, they may not elect to purchase such product, or if they purchase our products, they may not do so at prices and volume levels that are profitable for us.

If we or our collaborators, manufacturers or service providers fail to comply with regulatory laws and regulations, we or they could be subject to enforcement actions, which could affect our ability to market and sell our products and may harm our reputation.

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:

warning letters;

product recalls or public notification or medical product safety alerts to healthcare professionals;

restrictions on, or prohibitions against, marketing our products;

restrictions on importation or exportation of our products;

suspension of review or refusal to approve pending 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.

Any drugs we develop may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare

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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, our programs are currently in the early 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 our programs are in the early 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, 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 for pharmaceutical products. If the price we are able to charge for any products we develop is inadequate in light of our development and other costs, our profitability could be adversely affected.

We currently expect that any drugs we develop may need to be administered under the supervision of a physician. Under currently applicable United States law, drugs that are not usually self-administered may be eligible for coverage by the Medicare 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 standard of medical practice;

they are not excluded as immunizations; and

they have been approved by the FDA.

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 health care 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 profitable reimbursement rates from both government-funded and private payors for new drugs that we develop 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 will continue to affect the business and financial condition of pharmaceutical and biopharmaceutical companies. A number of legislative and regulatory proposals to change the healthcare system in the United States and other major healthcare markets have been proposed in recent years. These proposals have included prescription drug benefit legislation that was enacted and took effect in January 2006 and healthcare reform legislation recently enacted by certain states.

Further federal and state legislative and regulatory developments are possible 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 drug candidates that we may successfully develop.

Another development that may affect the pricing of drugs is Congressional action regarding drug reimportation into the United States. Recent proposed legislation has been introduced in Congress that, if enacted, would permit more widespread re-importation of drugs from foreign countries into the United States. This could include re-importation from foreign countries where the drugs are sold at lower prices than in the United States. Such legislation, or similar regulatory changes, could lead to a decrease in the price we

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receive for any approved products, which, in turn, could impair our ability to generate revenue. Alternatively, in response to legislation such as this, we might elect not to seek approval for or market our products in foreign jurisdictions in order to minimize the risk of re-importation, which could also reduce the revenue we generate from our product sales.

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, 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 indications for which they may be used, or suspension or withdrawal of approvals. 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 drug 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 and development 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 and, until recently, in Germany that are required for our research and development 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 facility comply with the relevant guidelines of the City of Cambridge and the Commonwealth of Massachusetts and the procedures we employed in our German facility complied with the standards mandated by applicable German laws and guidelines. Although we believe that our safety procedures for handling and disposing of these materials comply with the standards mandated by applicable regulations, the risk of accidental contamination or injury from these materials cannot be eliminated. If an accident occurs, we could be held liable for resulting damages, which could be substantial. We are also subject to numerous environmental, health and workplace safety laws and regulations, including those governing laboratory procedures, exposure to blood-borne pathogens and the handling of biohazardous materials.

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

Risks Related to Patents, Licenses and Trade Secrets

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

Our success depends, in part, on our ability to protect proprietary methods and technologies that we develop under the patent and other intellectual property laws of the 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

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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. Moreover, third parties or the 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. Adding to the uncertainty of our current intellectual property portfolio and our ability to secure and enforce future patent rights are the outcome of a legal dispute surrounding the implementation of certain continuation and claims rules promulgated by the USPTO, which were scheduled to take effect November 1, 2007, but which are now enjoined and on appeal, and the outcome of Congressional efforts to reform the Patent Act of 1952. 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 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, Isis, MIT, the Whitehead Institute for Biomedical Research, Max Planck Innovation, Stanford University and Tekmira. 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.

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

RNA interference 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, when, to whom, and with what claims. It is likely that there will be

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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 series in the European Patent Office, or EPO, and in Australia and Germany. 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 that we may need to apply to our siRNA drug 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. Furthermore, in connection with a license agreement, we have agreed to indemnify the licensor for costs incurred in connection with litigation relating to intellectual property rights. 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 the 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 limit our ability to continue our operations.

If any parties successfully claim that our creation or use of proprietary technologies infringes upon 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 could lose license rights that are necessary for developing and protecting our RNAi technology and any related product candidates that we develop, or we could lose certain exclusive rights to grant sublicenses.

Our current licenses impose, and any future licenses we enter into are likely to impose, various development, commercialization, funding, royalty, diligence, sublicensing, insurance and other obligations on us. If we breach any of these obligations, 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. 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.

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

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

Risks Related to Competition

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

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

- much greater financial, technical and human resources than we have at every stage of the discovery, development, manufacture and commercialization of products;
- more extensive experience in pre-clinical testing, conducting clinical trials, obtaining regulatory approvals, and in manufacturing and marketing 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. For instance, we are currently evaluating RNAi therapeutics for RSV, liver cancer, hypercholesterolemia and HD, and have a number of additional discovery programs targeting other diseases. Virazole and Synagis are currently marketed for the treatment of certain RSV patients, and numerous drugs are currently marketed or used for the treatment of liver cancer, hypercholesterolemia and HD as well. These drugs, or other of our competitors products, may be more effective, safer, less expensive or marketed and sold more effectively, than any products we develop.

If we successfully develop drug 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

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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 drug candidates. 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 drug candidates noncompetitive, obsolete or uneconomical.

We face competition from other companies that are working to develop novel drugs 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 will be adversely affected.

In addition to the competition we face from competing drugs in general, we also face competition from other companies working to develop novel drugs using technology that competes more directly with our own. We are aware of several 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., Calando Pharmaceuticals, Inc., Tekmira, Quark Biotech, Inc. 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. Merck was one of our collaborators and a licensee under our intellectual property for specified disease targets until September 2007, at which time we and Merck agreed to terminate our collaboration. As a result of its acquisition of Sirna Therapeutics Inc. in December 2006, and in light of the mutual termination of our collaboration, Merck, which has substantially more resources and experience in developing drugs than we do, may become a direct competitor.

In addition, as a result of agreements that we have entered into, Roche and Takeda have obtained, and Novartis has the right to obtain, broad, non-exclusive licenses 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 product candidates, antisense drugs target messenger RNAs, or mRNAs, in order to suppress the activity of specific genes. Isis is currently marketing an antisense drug and has several antisense drug candidates in clinical trials. 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 may 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 our expected stock volatility.

Our stock price may fluctuate for many reasons, including as a result of public announcements regarding the progress of our

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development efforts, the addition or departure of our key personnel, variations in our quarterly operating results and changes in market valuations of pharmaceutical and biotechnology companies. Recently, 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.

Novartis ownership of our common stock could delay or prevent a change in corporate control or cause a decline in our common stock should Novartis decide to sell all or a portion of its shares.

As of September 30, 2008, Novartis holds 13.2% of our outstanding common stock and has the right to maintain its ownership percentage through the expiration or termination of our broad alliance. 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.

In addition, if Novartis decides to sell all or a portion of its shares in a rapid or disorderly manner, our stock price could be negatively impacted.

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.

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ITEM 6. EXHIBITS

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.

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SIGNATURES

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

ALNYLAM PHARMACEUTICALS, INC.

Date: November 7, 2008

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

Date: November 7, 2008

/s/ Patricia L. Allen
Patricia L. Allen
Vice President of Finance and Treasurer
(Principal Financial and Accounting Officer)