

ALNYLAM PHARMACEUTICALS, INC.

Form 10-K

February 26, 2010

**Table of Contents**

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

**Form 10-K**

- ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES  
EXCHANGE ACT OF 1934**  
**For the fiscal year ended December 31, 2009**
- OR**
- TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES  
EXCHANGE ACT OF 1934**  
**For the transition period from        to**

**Commission File Number 000-50743**

**ALNYLAM PHARMACEUTICALS, INC.**  
*(Exact Name of Registrant as Specified in Its Charter)*

**Delaware**  
*(State or Other Jurisdiction of  
Incorporation or Organization)*

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

**300 Third Street, Cambridge, MA 02142**  
*(Address of Principal Executive Offices) (Zip Code)*  
**Registrant's telephone number, including area code: (617) 551-8200**  
**Securities registered pursuant to Section 12(b) of the Act:**

<b>Title of Each Class</b>	<b>Name of Each Exchange on Which Registered</b>
<b>Common Stock, \$0.01 par value per share</b>	<b>The Nasdaq Global Market</b>

**Securities registered pursuant to Section 12(g) of the Act: None**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes  No

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes  No

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

Edgar Filing: ALNYLAM PHARMACEUTICALS, INC. - Form 10-K

required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes  No

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

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of the registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

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  Accelerated filer  Non-accelerated filer  Smaller reporting company   
(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 Act). Yes  No

The aggregate market value of the voting Common Stock held by non-affiliates of the registrant, based on the last sale price of the registrant's Common Stock at the close of business on June 30, 2009, was \$916,012,936.

As of January 31, 2010, the registrant had 41,837,475 shares of Common Stock, \$0.01 par value per share, outstanding.

#### **DOCUMENTS INCORPORATED BY REFERENCE**

Portions of the registrant's definitive proxy statement for its 2010 annual meeting of stockholders, to be filed pursuant to Regulation 14A with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year end of December 31, 2009, are incorporated by reference into Part II, Item 5 and Part III of this Form 10-K.

---

**ALNYLAM PHARMACEUTICALS, INC.  
ANNUAL REPORT ON FORM 10-K  
For the Year Ended December 31, 2009**

**TABLE OF CONTENTS**

**PART I**

<u>ITEM 1.</u>	<u>BUSINESS</u>	2
<u>ITEM 1A.</u>	<u>RISK FACTORS</u>	43
<u>ITEM 1B.</u>	<u>UNRESOLVED STAFF COMMENTS</u>	67
<u>ITEM 2.</u>	<u>PROPERTIES</u>	67
<u>ITEM 3.</u>	<u>LEGAL PROCEEDINGS</u>	67
<u>ITEM 4.</u>	<u>SUBMISSION OF MATTERS TO A VOTE OF SECURITY HOLDERS</u>	67

**PART II**

<u>ITEM 5.</u>	<u>MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES</u>	68
<u>ITEM 6.</u>	<u>SELECTED CONSOLIDATED FINANCIAL DATA</u>	70
<u>ITEM 7.</u>	<u>MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS</u>	71
<u>ITEM 7A.</u>	<u>QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK</u>	101
<u>ITEM 8.</u>	<u>FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA</u>	102
<u>ITEM 9.</u>	<u>CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE</u>	143
<u>ITEM 9A.</u>	<u>CONTROLS AND PROCEDURES</u>	143
<u>ITEM 9B.</u>	<u>OTHER INFORMATION</u>	143

**PART III**

<u>ITEM 10.</u>	<u>DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE</u>	143
<u>ITEM 11.</u>	<u>EXECUTIVE COMPENSATION</u>	143
<u>ITEM 12.</u>	<u>SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS</u>	144
<u>ITEM 13.</u>	<u>CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE</u>	144
<u>ITEM 14.</u>	<u>PRINCIPAL ACCOUNTANT FEES AND SERVICES</u>	144

**PART IV**

<u>ITEM 15.</u>	<u>EXHIBITS AND FINANCIAL STATEMENT SCHEDULES</u>	144
<b><u>SIGNATURES</u></b>		145
<u>EX-10.9 Forms of Incentive Stock Option Agreement and Nonstatutory Stock Option Agreement</u>		
<u>EX-10.16 2010 Annual Incentive Program</u>		
<u>EX-10.39 Collaboration Agreement entered into as of October 29, 2009</u>		
<u>EX-10.40 First Amendment to License and Collaboration Agreement entered into as of November 2, 2009</u>		
<u>EX-21.1 Subsidiaries of the Registrant</u>		
<u>EX-23.1 Consent of PricewaterhouseCoopers LLP</u>		
<u>EX-23.2 Consent of Ernst &amp; Young LLP, Independent Auditors of Regulus Therapeutics Inc.</u>		
<u>EX-31.1 Section 302 Certification of the Chief Executive Officer</u>		
<u>EX-31.2 Section 302 Certification of the Vice President of Finance and Treasurer</u>		
<u>EX-32.1 Section 906 Certification of the Chief Executive Officer</u>		

Edgar Filing: ALNYLAM PHARMACEUTICALS, INC. - Form 10-K

EX-32.2 Section 906 Certification of the Vice President of Finance and Treasurer

EX-99.1 Regulus Therapeutics Inc.'s Financial Statements

**Table of Contents**

*This annual report on Form 10-K contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, that involve risks and uncertainties. All statements other than statements relating to historical matters should be considered forward-looking statements. When used in this report, the words believe, expect, anticipate, will, plan, target, and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these words. Our actual results could differ materially from those discussed in the forward-looking statements as a result of a number of important factors, including the factors discussed in this annual report on Form 10-K, including those discussed in Item 1A of this report under the heading Risk Factors, and the risks discussed in our other filings with the Securities and Exchange Commission. Readers are cautioned not to place undue reliance on these forward-looking statements, which reflect management's analysis, judgment, belief or expectation only as of the date hereof. We explicitly disclaim any obligation to update these forward-looking statements to reflect events or circumstances that arise after the date hereof.*

**PART I**

**ITEM 1. BUSINESS**

**Overview**

We are a biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. RNAi is a naturally occurring biological pathway within cells for selectively silencing and regulating the expression of specific genes. Since many diseases are caused by the inappropriate activity of specific genes, the ability to silence genes selectively through RNAi could provide a new way to treat a wide range of human diseases. We believe that drugs that work through RNAi have the potential to become a broad new class of drugs, like small molecule, protein and antibody drugs. Using our intellectual property and the expertise we have built in RNAi, we are developing a set of biological and chemical methods and know-how that we apply in a systematic way to develop RNAi therapeutics for a variety of diseases.

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. We are working to develop RNAi therapeutics that are delivered directly to specific sites of disease, as well as RNAi therapeutics that are administered systemically through the bloodstream by intravenous, subcutaneous or intramuscular approaches. 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. In February 2008, we reported positive results from our Phase II experimental RSV infection clinical trial, referred to as the GEMINI study. In July 2009, we and Cubist Pharmaceuticals, Inc., or Cubist, reported results from a Phase IIa clinical trial assessing the safety and tolerability of aerosolized ALN-RSV01 versus placebo in adult lung transplant patients naturally infected with RSV. This study achieved its primary objective of demonstrating the safety and tolerability of ALN-RSV01. In February 2010, we initiated a multi-center, global, randomized, double-blind, placebo-controlled Phase IIb clinical trial to evaluate the clinical efficacy endpoints, as well as safety, of aerosolized ALN-RSV01 in adult lung transplant patients naturally infected with RSV. The objective of this Phase IIb study is to repeat and extend the clinical results observed in the Phase IIa study.

We have formed collaborations with Cubist and Kyowa Hakko Kirin Co., Ltd., or Kyowa Hakko Kirin, for the development and commercialization of RNAi products for RSV. We have an agreement to jointly develop and commercialize certain RNAi products for RSV with Cubist in North America. Cubist has responsibility for developing and commercializing any such products in the rest of the world outside of Asia, and Kyowa Hakko Kirin has the responsibility for developing and commercializing any RNAi products for RSV in Asia. In November 2009, we and

Cubist agreed that Alnylam would move forward with the development of ALN-RSV01, and together we would focus our collaboration and joint development efforts on ALN-RSV02, a second-generation compound, intended for use in pediatric patients. We and Cubist each bears one-half of the related development costs for ALN-RSV02. We are also continuing to develop ALN-RSV01 for adult transplant patients at our sole discretion and expense. Cubist has the right to resume the collaboration on ALN-RSV01 in the future, which right may be exercised for a specified period of time following the completion of our Phase IIb study, subject to the payment by

**Table of Contents**

Cubist of an opt-in fee representing reimbursement of an agreed upon percentage of certain of our development expenses for ALN-RSV01.

In March 2009, we initiated a Phase I study for ALN-VSP, our second clinical program and our first systemically delivered RNAi therapeutic candidate. We are developing ALN-VSP for the treatment of liver cancers, including hepatocellular carcinoma, or HCC, and other solid tumors with liver involvement. This Phase I study is a multi-center, open label, dose escalation study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of intravenous ALN-VSP in up to approximately 55 patients with advanced solid tumors with liver involvement, including HCC.

In December 2009, we filed regulatory applications to initiate a clinical trial for ALN-TTR01, our second systemically delivered RNAi therapeutic candidate. We are developing ALN-TTR, which targets the transthyretin, or TTR, gene, for the treatment of TTR-mediated amyloidosis, or ATTR. We plan to initiate a Phase I trial of ALN-TTR01 in ATTR patients in the first half of 2010. ALN-TTR01 employs a first generation lipid nanoparticle, or LNP, formulation. In parallel, we are also advancing ALN-TTR02 utilizing second-generation LNPs.

In January 2010, we announced that we expect ALN-PCS, a systemically delivered RNAi therapeutic candidate for the treatment of hypercholesterolemia, to be our next clinical candidate. ALN-PCS targets a gene called proprotein convertase subtilisin/kexin type 9, or PCSK9.

We are also working on a number of programs in pre-clinical development, including ALN-HTT, an RNAi therapeutic candidate targeting the huntingtin gene, for the treatment of Huntington's disease, which we are developing in collaboration with Medtronic, Inc., or Medtronic. We have additional discovery programs for RNAi therapeutics for the treatment of a broad range of diseases.

In addition, we are working internally and with third-party collaborators to develop capabilities to deliver our RNAi therapeutics directly to specific sites of disease, such as the delivery of ALN-RSV to the lungs. We are also working to extend our capabilities to advance the development of RNAi therapeutics that are administered systemically by intravenous, subcutaneous or intramuscular approaches. Over the past 12 to 18 months, we have made several of what we believe to be major advances relating to the delivery of RNAi therapeutics, both internally and together with our collaborators. We have numerous RNAi therapeutic delivery collaborations and intend to continue to collaborate with government, academic and corporate third parties to evaluate different delivery options.

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 as well as those claiming crucial chemical modifications and promising delivery technologies. We believe that no other company possesses a portfolio of such broad and exclusive rights to the patents and patent applications required for the commercialization of RNAi therapeutics. Given the importance of our intellectual property portfolio to our business operations, we intend to vigorously enforce our rights and defend against challenges that have arisen or may arise in this area.

In addition, our expertise in RNAi therapeutics and broad intellectual property estate have allowed us to form alliances with leading companies, including Isis Pharmaceuticals, Inc., or Isis, Medtronic, Novartis Pharma AG, or Novartis, Biogen Idec Inc., or Biogen Idec, F. Hoffmann-La Roche Ltd, or Roche, Takeda Pharmaceutical Company Limited, or Takeda, Kyowa Hakko Kirin and Cubist. We have also entered into contracts with government agencies, including the National Institute of Allergy and Infectious Diseases, or NIAID, a component of the National Institutes of Health, or NIH. We have established collaborations with and, in some instances, received funding from major medical and disease associations. Finally, to further enable the field and monetize our intellectual property rights, we



also grant licenses to biotechnology companies for the development and commercialization of RNAi therapeutics for specified targets in which we have no direct strategic interest under our InterfeRx™ program, and to research companies that commercialize RNAi reagents or services under our research product licenses.

We also seek opportunities to form new ventures in areas outside our core strategic focus. For example, during 2009, we presented new data regarding the application of RNAi technology to improve the manufacturing processes for biologics, which is comprised of recombinant proteins, monoclonal antibodies and vaccines. This initiative,

## **Table of Contents**

which we are advancing in an internal effort referred to as Alnylam Biotherapeutics, has the potential to create new business opportunities. Additionally, during 2007, we and Isis established Regulus Therapeutics Inc., formerly Regulus Therapeutics LLC, or Regulus, a company focused on the discovery, development and commercialization of microRNA-based therapeutics. Because microRNAs are believed to regulate whole networks of genes that can be involved in discrete disease processes, microRNA-based therapeutics represent a possible new approach to target the pathways of human disease. Given the broad applications for RNAi technology, we believe additional opportunities exist for new ventures.

Below is a list of some of our key developments in 2009 and early 2010.

### **2009 and Early 2010 Key Developments**

#### ***Product Pipeline and Scientific Developments***

We advanced development of our ALN-RSV program focused on the treatment of RSV infection. We and Cubist presented complete data from a Phase IIa randomized, double-blind study of inhaled ALN-RSV01 or placebo in RSV-infected adult lung transplant patients. This study achieved its primary objective of demonstrating safety and tolerability of ALN-RSV01. In order to repeat and extend the Phase IIa results, we recently initiated a multi-center, global, randomized, double-blind, placebo-controlled Phase IIb study of ALN-RSV01 in RSV-infected adult lung transplant patients.

We initiated a Phase I multi-center, open label, dose escalation trial to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of intravenous ALN-VSP in patients with advanced solid tumors with liver involvement, including HCC. ALN-VSP is our first systemic RNAi program and represents our first clinical program in oncology.

We filed regulatory applications to initiate a clinical trial for our ALN-TTR program for ATTR. We expect to initiate a Phase I trial of ALN-TTR01 in ATTR patients in the first half of 2010. ALN-TTR01 is a systemically delivered RNAi therapeutic that employs first generation LNPs. In parallel, we are also advancing ALN-TTR02 utilizing second generation LNPs.

We continued to advance additional development and pre-clinical programs including ALN-PCS, an RNAi therapeutic targeting PCSK9 for the treatment of hypercholesterolemia. We expect that ALN-PCS will be our next clinical candidate. In addition, in collaboration with Medtronic, we continued to advance ALN-HTT, an RNAi therapeutic targeting the huntingtin gene for Huntington's disease.

We have made what we believe to be several major advances relating to the delivery of RNAi therapeutics. In collaboration with scientists at the Massachusetts Institute of Technology, or MIT, and, separately, in collaboration with scientists at AICana Technologies, Inc., or AICana, Tekmira Pharmaceuticals Corporation, or Tekmira, and The University of British Columbia, or UBC, we published on the discovery of novel lipids that enable formulation of second generation LNPs with markedly enhanced gene silencing potency, with *in vivo* effects achieved at doses as low as 0.01 mg/kg in rodents and non-human primates.

We formed new collaborations focused on the delivery of RNAi therapeutics. We formed a new research collaboration with scientists at UBC and AICana, in addition to Tekmira, focused on the discovery of novel cationic lipids for use in LNPs for the systemic delivery of RNAi therapeutics. We also established a new collaboration with Isis focused on the development of single-stranded RNAi, or ssRNAi, technology.

We launched Alnylam Biotherapeutics, which is an internal effort regarding the application of RNAi technology to improve the manufacturing processes for biologics. In particular, Alnylam Biotherapeutics is advancing RNAi technologies to improve the quantity and quality of biologics manufacturing processes using mammalian cell culture, such as Chinese hamster ovary, or CHO, cells. This RNAi technology potentially could be applied to the improvement of manufacturing processes for existing marketed drugs, new drugs in development and for the emerging biosimilars market.

During 2009, our scientists and scientists from Regulus demonstrated continued scientific leadership with the publication of 24 peer-reviewed scientific papers in some of the world's top journals.

## **Table of Contents**

### ***Business Execution***

We formed a strategic collaboration with Cubist for the development and commercialization of our ALN-RSV program. Our collaboration with Cubist is a 50-50 co-development and profit share arrangement in North America, and a milestone- and royalty-bearing license arrangement in the rest of the world outside of Asia, where we collaborate on the ALN-RSV program with Kyowa Hakko Kirin. In November 2009, we and Cubist agreed that Alnylam would move forward with the development of ALN-RSV01 in adult transplant patient populations, and together we would focus our collaboration and joint development efforts on ALN-RSV02 in pediatric patients.

Novartis elected to extend our RNAi therapeutics collaboration for a fifth and final planned year, through October 2010, resulting in continued research and development funding to us.

We and Roche initiated the drug discovery phase of our 2007 alliance. In addition, we received a milestone payment from Roche related to the initiation of pre-investigational new drug application, or IND, studies for an RNAi therapeutic product candidate.

We and Isis continued our investment in Regulus with a \$20.0 million Series A preferred equity financing.

Regulus, of which we own 49%, formed a new collaboration with GlaxoSmithKline, or GSK, to develop and commercialize microRNA-based therapeutics targeting miR-122 in all fields, with hepatitis C virus, or HCV, infection, as the lead indication. This new collaboration includes the potential for Regulus to earn more than \$150.0 million in upfront and milestone payments, in addition to royalties, on worldwide sales of products, if any, as Regulus and GSK advance microRNA-based therapeutics targeting miR-122.

### ***Intellectual Property***

We advanced our intellectual property estate, receiving over 40 new patents worldwide during 2009.

We joined GSK in donating intellectual property to a patent pool for neglected tropical diseases.

We joined the Max Planck Society in taking legal action toward the Whitehead Institute for Biomedical Research, or Whitehead. Also named in the suit are MIT and the Board of Trustees of the University of Massachusetts, or UMass. The complaint alleges that Whitehead has breached its contractual obligations to Max Planck and us in the manner in which it is prosecuting the so-called Tuschl I patent applications and in its fiduciary duty to all of the co-owners of the Tuschl I patent series.

### ***RNA Interference***

RNAi is a natural biological pathway that occurs within cells and can be harnessed to selectively silence the activity of specific genes. The discovery of RNAi first occurred in plants and worms in 1998, and two of the scientists who made this discovery, Dr. Andrew Fire and Dr. Craig Mello, received the 2006 Nobel Prize for Physiology or Medicine.

### ***Opportunity for Therapeutics Based on RNAi***

Beginning in 1999, our scientific founders described and provided evidence that the RNAi mechanism occurs in mammalian cells and that its immediate trigger is a type of molecule known as a small interfering RNA, or siRNA. They showed that laboratory-synthesized siRNAs could be introduced into the cell and suppress production of specific

target proteins by cleaving and degrading the messenger RNA, or mRNA, of the specific gene that encodes that specific protein. Because it is possible to design and synthesize siRNAs specific to any gene of interest, the entire human genome is accessible to RNAi, and we therefore believe that RNAi therapeutics have the potential to become a broad new class of drugs.

In May 2001, one of our scientific founders, Thomas Tuschl, Ph.D., published the first scientific paper demonstrating that siRNAs can be synthesized in the laboratory using chemical or biochemical methods and when introduced, or delivered, into mammalian cells can silence the activity of a specific gene. Since the Tuschl publication, the use of siRNAs has been broadly adopted by academic and industrial researchers for the

## **Table of Contents**

fundamental study of the function of genes. This has resulted in a significant number of publications focused on the use of RNAi and has made the 2001 paper one of the most cited papers in basic biologic research. Reflecting this, siRNAs are a growing segment of the market for research reagents and related products and services.

Beyond its use as a basic research tool, we believe that RNAi can form the basis of a completely new class of drugs for the treatment of disease. Drugs based on the RNAi mechanism could offer numerous opportunities and benefits, which may include:

**Ability to target proteins that cannot be targeted effectively by existing drug classes.** Over the last decade, the understanding of human disease has advanced enormously and many proteins have been identified that play fundamental roles in human disease. Paradoxically, greater than 80% of these key proteins cannot be targeted effectively with existing drug approaches like small molecules or proteins such as monoclonal antibodies. These so called undruggable targets are potentially accessible to siRNAs as they are made by mRNAs that can be targeted with RNAi.

**Ability to treat a broad range of diseases.** The ability to make siRNAs that target virtually any gene to suppress the production of virtually any protein whose presence or activity causes disease suggests a broad potential for application in a wide range of diseases.

**Inherently potent mechanism of action.** We expect the inherent catalytic nature of the RNAi mechanism to allow for a high degree of potency and durability of effect for RNAi-based therapeutics, which we believe distinguishes RNAi from other approaches.

**Simplified discovery of product candidates.** In contrast to the often arduous and slow drug discovery process for proteins and small molecules, the identification of siRNA product candidates has been, and we expect will continue to be, much simpler, quicker and less costly because it involves relatively standard processes that are directed by the known gene target sequences and can be applied in a similar fashion to many successive product candidates.

We have reported on our advances in developing siRNAs as potential drugs in a large number of peer-reviewed publications and meetings, including publications by Alnylam scientists in the journals *Nature*, *Cell*, *Nature Medicine*, *Nature Biotechnology* and *Proceedings of the National Academy of Sciences*, or *PNAS*.

## **Our Product Platform**

Our product platform provides a capability for a systematic approach to identifying RNAi therapeutic candidates through sequence selection, potency selection, stabilization by chemical modification, improvement of biodistribution and cellular uptake by various chemical conjugates and formulations. Key to the therapeutic application of siRNAs is the ability to successfully deliver siRNAs to target tissues and achieve cellular uptake of the siRNA into the inside of the cell where the RNAi machinery, called RNA-induced silencing complex, or RISC, is active. In some tissues, including the lung and central nervous system, the direct RNAi delivery approach, which employs the direct or local application of siRNAs, achieves cellular uptake and gene knockdown. For other tissues, such as the liver, systemic RNAi delivery has been employed, where tissue access comes via intravenous or subcutaneous injection of the siRNA into the bloodstream and where cellular uptake can be achieved by the conjugation of the siRNA with other molecules, such as small chemical groups, or by formulation with other biomaterials, such as LNPs. siRNA delivery is a key focus for our internal research team and is also the focus of numerous current government, academic and corporate collaborations. We have demonstrated RNAi therapeutic activity towards multiple genes, in multiple organs and in multiple species, including humans, as demonstrated by our results in the GEMINI trial for ALN-RSV01.

We believe that we have made considerable progress in developing our product platform, as documented in several recent publications. Over the past 12 to 18 months, we have made several of what we believe to be major advances relating to the delivery of RNAi therapeutics, both internally and together with our collaborators. The first relates to the discovery of new LNP compositions that provide dramatic improvements in the potency of gene silencing as compared to first generation LNPs. Additionally, we believe we have discovered an important *in vivo* mechanism for delivery relating to the role of endogenous apolipoprotein E, or ApoE, a plasma protein involved in lipoprotein metabolism, in the delivery of certain LNPs into the cytoplasm of certain cells. The latter discovery has

## **Table of Contents**

allowed the specific targeting of LNPs and allows the possibility of delivery beyond the liver. We discuss these advances and our overall delivery efforts in more detail below in the section entitled Delivery Initiatives. With the progress we have made to date and expect to make in the future, we believe we will be well positioned to pursue multiple therapeutic opportunities.

Our progress has enabled us to advance a number of development programs for RNAi therapeutics that are administered directly to diseased tissues, including ALN-RSV01 and ALN-HTT. Our progress in achieving delivery of RNAi therapeutics through systemic RNAi was demonstrated by the advancement in early 2009 of our first systemically delivered RNAi therapeutic candidate ALN-VSP, for the treatment of liver cancers, to the clinic, and the filing of regulatory applications in December 2009 to initiate a clinical trial for ALN-TTR01, our second systemically delivered RNAi therapeutic candidate, for the treatment of ATTR. ALN-VSP and ALN-TTR01 both utilize a first generation LNP formulation known as stable nucleic acid-lipid particles, or SNALP, developed in collaboration with Tekmira. In parallel with ALN-TTR01, we are also advancing ALN-TTR02 utilizing the newer second-generation LNPs. In addition, we have published pre-clinical results from development programs for other systemically delivered RNAi therapeutic candidates, including ALN-PCS, for the treatment of hypercholesterolemia, which we recently identified as our next clinical candidate. ALN-PCS is being advanced using second-generation LNPs for systemic delivery. We recognize, however, that challenges remain with respect to the development of RNAi-based therapeutics, including achieving effective delivery of siRNAs to target cells and tissues, and we therefore regard further development of our product platform as an ongoing priority.

## **Our Product Pipeline**

The following is a summary of our development programs as of January 31, 2010:

Our most advanced program is focused on the treatment of RSV, a virus that infects the respiratory tract. In January 2008, we completed our GEMINI study, a Phase II clinical trial designed to evaluate the safety, tolerability and anti-viral activity of ALN-RSV01 in adult subjects experimentally infected with RSV. In July 2009, we and Cubist reported results from a Phase IIa clinical trial assessing the safety and tolerability of aerosolized ALN-RSV01 versus placebo in adult lung transplant patients naturally infected with RSV. This study achieved its primary objective of demonstrating the safety and tolerability of ALN-RSV01. In February 2010, we initiated a multi-center, global, randomized, double-blind, placebo-controlled Phase IIb clinical trial to evaluate the clinical efficacy endpoints as well as safety of aerosolized ALN-RSV01 in adult lung transplant patients naturally infected with RSV. The objective of this Phase IIb study is to repeat and extend the clinical results observed in the Phase IIa study.

We have formed collaborations with Cubist and Kyowa Hakko Kirin for the development and commercialization of RNAi products for RSV. We have an agreement to jointly develop and commercialize certain RNAi products for RSV with Cubist in North America. Cubist has responsibility for developing and



## **Table of Contents**

commercializing any such products in the rest of the world outside of Asia, and Kyowa Hakko Kirin has the responsibility for developing and commercializing any RNAi products for RSV in Asia. In November 2009, we and Cubist agreed that Alnylam would move forward with the development of ALN-RSV01, and together we would focus our collaboration and joint development efforts on ALN-RSV02, a second-generation compound, intended for use in pediatric patients. We and Cubist each bears one-half of the related development costs for ALN-RSV02. We are also continuing to develop ALN-RSV01 for adult transplant patients at our sole discretion and expense. Cubist has the right to resume the collaboration on ALN-RSV01 in the future, which right may be exercised for a specified period of time following the completion of our Phase IIb trial, subject to the payment by Cubist of an opt-in fee representing reimbursement of an agreed upon percentage of certain of our development expenses for ALN-RSV01.

In March 2009, we initiated a Phase I study for ALN-VSP, our second clinical program and our first systemically delivered RNAi therapeutic candidate. We are developing ALN-VSP for the treatment of liver cancers, including HCC, and other solid tumors with liver involvement. This Phase I study is a multi-center, open label, dose escalation study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of intravenous ALN-VSP in up to approximately 55 patients with advanced solid tumors with liver involvement, including HCC.

In December 2009, we filed regulatory applications to initiate a clinical trial for ALN-TTR01, our second systemically delivered RNAi therapeutic candidate. We are developing ALN-TTR, which targets the TTR gene, for the treatment of ATTR. ALN-TTR targets wild-type and all mutant forms of TTR, and therefore is a potential therapeutic for the treatment of all forms of ATTR, including familial amyloidotic polyneuropathy, or FAP, and familial amyloidotic cardiomyopathy, or FAC. We plan to initiate a Phase I trial of ALN-TTR01 in ATTR patients in the first half of 2010. ALN-TTR01 employs a first generation LNP formulation. In parallel, we are also advancing ALN-TTR02 utilizing second-generation LNPs.

In January 2010, we announced that we expect ALN-PCS, a systemically delivered RNAi therapeutic candidate for the treatment of hypercholesterolemia, to be our next clinical candidate. ALN-PCS targets a gene called PCSK9. We are also working on a number of programs in pre-clinical development, including ALN-HTT, an RNAi therapeutic candidate for the treatment of Huntington's disease, which we are developing jointly with Medtronic. We have additional discovery programs for RNAi therapeutics for the treatment of a broad range of diseases.

We have spent substantial funds over the past three years to develop our product pipeline and expect to continue to do so in the future. We incurred research and development costs of \$108.7 million in 2009, \$96.9 million in 2008 and \$120.7 million in 2007. Research and development costs in 2007 included \$27.5 million in license fees paid to certain entities, primarily Isis, in connection with our alliance with Roche.

## **Development Programs**

### ***Respiratory Syncytial Virus (RSV) Infection***

**Market Opportunity.** RSV is a highly contagious virus that causes infections in both the upper and lower respiratory tract. RSV infects nearly every child by the age of two years and is responsible for a significant percentage of hospitalizations of infants, children with lung or congenital heart disease, the elderly and adults with immune-compromised systems, including lung transplant recipients. RSV infection typically results in cold-like symptoms, but can lead to more serious respiratory illnesses such as croup, pneumonia and bronchiolitis, and in extreme cases, severe illness and death. According to NIH, up to 125,000 children are hospitalized each year due to RSV infection. A study published in the *New England Journal of Medicine* estimates that over 170,000 elderly adults are hospitalized with RSV each year. In addition, experts estimate that the overall prevalence of lung transplants in the United States is between 8,000 to 10,000. The annual incidence of RSV infection in lung transplant patients can be up to ten percent.

**Current Treatments.** The only product currently approved for the treatment of RSV infection is Ribavirin, which is marketed as Virazole<sup>®</sup> by Valeant Pharmaceuticals International, or Valeant. However, this product is approved only for treatment of hospitalized infants and young children with severe lower respiratory tract infections

**Table of Contents**

due to RSV. Moreover, administration of the drug is complicated and requires elaborate environmental reclamation devices because of potential harmful effects on healthcare personnel exposed to the drug.

Two other products, a monoclonal antibody known as Synagis® and an immune globulin called RespiGam™, have been approved for the *prevention* of severe lower respiratory tract disease caused by RSV in infants at high risk of such disease. Neither of these products is approved for *treatment* of an existing RSV infection.

**Alnylam Program.** In June 2007, we initiated the GEMINI study, a double-blind, placebo-controlled, randomized Phase II trial designed to evaluate the safety, tolerability and anti-viral activity of ALN-RSV01 in adult subjects experimentally infected with RSV. In total, 88 subjects were randomized one-to-one to receive either ALN-RSV01 or placebo treatment prior to and after experimental infection with a wild-type clinical strain of RSV. In February 2008, we reported positive results from the GEMINI study. ALN-RSV01 was found to be safe and well tolerated and demonstrated statistically significant anti-viral activity, including an approximate 40% reduction in viral infection rate and a 95% increase in infection-free patients ( $p < 0.01$ ), as compared to placebo.

In July 2009, we and Cubist reported results from a Phase IIa clinical trial assessing the safety and tolerability of aerosolized ALN-RSV01 versus placebo in adult lung transplant patients naturally infected with RSV. In total, 24 patients confirmed with RSV infection were randomized two-to-one to receive inhaled ALN-RSV01 or placebo once daily for three consecutive days. The study achieved its primary objective of demonstrating the safety and tolerability of ALN-RSV01. In particular, there were no drug-related serious adverse events or discontinuations, and there were no clinically significant differences in the overall adverse event profile between ALN-RSV01 and placebo. Importantly, there was no evidence of disease exacerbation related to ALN-RSV01 treatment. At the 90-day endpoint, all patients survived and the incidence of intubation, new respiratory infection, or acute rejection was comparable across ALN-RSV01 and placebo groups. In addition, 90-day clinical data were collected. The study was not powered to demonstrate clinical outcomes due to the small sample size and, accordingly, such data were therefore considered exploratory. Prospectively defined clinical secondary endpoints at 90 days included recovery of lung function (forced expiratory volume in the first second, or FEV<sub>1</sub>) as measured by spirometry and clinical determination of new or progressive bronchiolitis obliterans syndrome, or BOS. Based on the data from this small study, ALN-RSV01 treatment was associated with a statistically significant decrease in the total incidence of new or progressive BOS at 90 days compared to placebo ( $p = 0.02$ ) with 50% of placebo patients showing new or progressive BOS as compared with only 7.1% of ALN-RSV01-treated patients. Despite the small patient numbers, we believe that these data may be important since the incidence of BOS following RSV infection in lung transplant patients can be a predictor of graft failure and overall survival. The incidence of BOS in lung transplant patients infected with RSV results in approximately 50% mortality within three to five years of onset.

In February 2010, we initiated a multi-center, global, randomized, double-blind, placebo-controlled Phase IIb clinical trial to evaluate the clinical efficacy endpoints as well as safety of aerosolized ALN-RSV01 in adult lung transplant patients naturally infected with RSV. The objective of this Phase IIb study is to repeat and extend the clinical results observed in the Phase IIa study described above. This study is expected to enroll 76 adult lung transplant patients who will be randomized in a one-to-one drug to placebo ratio. The primary endpoint is reduction in the incidence of new or progressive BOS.

Prior to the GEMINI and Phase IIa studies, ALN-RSV01 was shown in pre-clinical testing to be effective in both preventing and treating RSV infection in mice when administered intranasally. ALN-RSV01 also showed no significant toxicities in animal toxicology studies performed to enable the filing of an IND. We submitted an 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 in both the United States and Europe. In these Phase I trials, ALN-RSV01 was found to be generally safe and well tolerated when administered by single or repeat administration at doses up to 150 milligrams intranasally or at doses up to 0.6 milligrams per kilogram by nebulizer. The results of our completed

ALN-RSV01 clinical trials have been presented at medical conferences. We also have an active program to identify second-generation RNAi-based RSV inhibitors, and have identified several candidates in pre-clinical studies. As discussed below, we and Cubist are focusing our collaboration and joint development efforts on ALN-RSV02, a second generation compound, intended for use in pediatric patients.

We have formed collaborations with Cubist and Kyowa Hakko Kirin for the development and commercialization of RNAi products for RSV. We have an agreement to jointly develop and commercialize

**Table of Contents**

certain RNAi products for RSV with Cubist in North America. Cubist has responsibility for developing and commercializing any such products in the rest of the world outside of Asia, and Kyowa Hakko Kirin has the responsibility for developing and commercializing any RNAi products for RSV in Asia. In November 2009, we and Cubist agreed that Alnylam would move forward with the development of ALN-RSV01, and together we would focus our collaboration and joint development efforts on ALN-RSV02, a second-generation compound, intended for use in pediatric patients. We and Cubist each bears one-half of the related development costs for ALN-RSV02. As described above, we are also continuing to develop ALN-RSV01 for adult transplant patients at our sole discretion and expense and have recently initiated a Phase IIb study. Cubist has the right to resume the collaboration on ALN-RSV01 in the future, which right may be exercised for a specified period of time following the completion of our Phase IIb trial, subject to the payment by Cubist of an opt-in fee representing reimbursement of an agreed upon percentage of certain of our development expenses for ALN-RSV01.

***Liver Cancer***

**Market Opportunity.** An estimated 700,000 patients worldwide are diagnosed with primary liver cancer each year. HCC is the most common form of liver cancer and is responsible for about 90% of primary malignant liver tumors in adults. HCC is the sixth most common cancer in the world and the third leading cause of cancer-related deaths globally. In addition to primary liver cancer patients, in whom the disease starts in the liver, another 500,000 patients are identified each year with secondary liver cancer, whereby the primary tumor of another tissue, such as colorectal, stomach, pancreatic, breast, lung or skin, has metastasized to the liver.

**Current Treatments.** The treatment options for liver cancer are dependent on the stage of disease, site of tumor and condition of the patient, but can include surgical resection, radiation, chemotherapy, chemoembolism, liver transplantation and various combinations of these approaches. In November 2007, the FDA approved Sorafenib, also called Nexavar<sup>®</sup>, for the treatment of un-resectable liver cancer. Even with relatively early diagnosis and resection, the prognosis remains very poor for liver cancer patients, who are often diagnosed late in their clinical course of disease. For primary liver cancer, with early diagnosis and a resectable tumor, the five-year disease free survival rate has been reported at approximately 20%. However, this applies only to about 15% of primary liver cancer patients. For most primary liver cancer patients, the disease is fatal within three to six months. The prognosis for secondary liver cancer is generally also very poor, due often to the late stage of the disease at the time of diagnosis and metastatic nature of the neoplasm. For example, in the absence of treatment, the prognosis for patients with hepatic colorectal metastases is extremely poor, with five-year survival rates of three percent or less. Among patients that can be treated with complete resection of hepatic colorectal metastases, only 30% to 40% will survive for five years following resection.

**Alnylam Program.** In December 2008, we submitted an IND to the FDA for ALN-VSP, our first systemically delivered RNAi therapeutic candidate for the treatment of liver cancers, including HCC, and other solid tumors with liver involvement. In March 2009, we initiated a Phase I, multi-center, open label, dose escalation study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of intravenous ALN-VSP in up to approximately 55 patients with advanced solid tumors with liver involvement, including HCC.

ALN-VSP contains two siRNAs formulated using a first generation LNP formulation known as SNALP, developed in collaboration with Tekmira. ALN-VSP is designed to target two genes critical in the growth and development of cancer: kinesin spindle protein, or KSP, and vascular endothelial growth factor, or VEGF. KSP is a key component of the cellular machinery that mediates chromosome separation during cell division, which is critical for tumor proliferation. As such, it represents an important target for blocking tumor growth. VEGF is a potent angiogenic factor that drives the development of blood vessels that are critical to ensuring adequate blood supply to the growing tumor.

Pre-clinical data in mouse tumor model studies have demonstrated efficacy of ALN-VSP, including suppression of these targeted genes, demonstration of an RNAi mechanism of action, formation of monoesters, a characteristic

feature of KSP inhibition, anti-angiogenic effects resulting from VEGF inhibition, tumor reduction and extension of survival. Moreover, suppression of KSP has been shown in both hepatocellular and colorectal carcinoma models, and in liver tumors as well as metastases at other sites.

## **Table of Contents**

We believe our strategy of using an RNAi therapeutic targeting two well-validated genes critical for tumor proliferation and survival has the potential of achieving meaningful clinical benefit for patients with liver cancer. In addition, we believe that this is the first dual targeting RNAi therapeutic program to advance to clinical development. This is an important milestone, as we view the ability to design and formulate multiple siRNAs against more than one target as a potentially attractive feature of our RNAi therapeutics platform, particularly in the setting of oncology drug development.

### ***TTR-Mediated Amyloidosis (ATTR)***

**Market Opportunity.** ATTR is a hereditary, systemic disease caused by a mutation in the TTR gene. The resulting abnormal protein is deposited as TTR-containing amyloid fibrils in extrahepatic tissues, including the peripheral nervous system and the heart, which leads to FAP and FAC, respectively. FAP is associated with severe pain and loss of autonomic nervous function, known as neuropathy, whereas FAC is associated with heart failure. Typical onset for ATTR is between the fourth and sixth decades of life and the disease is often fatal within five to 15 years of onset. In its severest form, ATTR represents a tremendous unmet medical need with significant morbidity and mortality. ATTR is an orphan, or rare, disease, affecting approximately 50,000 people worldwide.

**Current Treatments.** There are no existing disease-modifying treatments to address ATTR. Currently, liver transplantation is the only available treatment for FAP. However, only a subset of FAP patients qualify for this costly and invasive procedure and, even following liver transplantation, the disease continues to progress for many of these patients, presumably due to normal TTR being deposited into preexisting fibrils. Moreover, there is a shortage of donors to provide healthy livers for transplantation into eligible patients. There are currently no therapies available to treat FAC.

**Alnylam Program.** ALN-TTR is an RNAi therapeutic candidate targeting the TTR gene for the treatment of ATTR. TTR is a carrier for thyroid hormone and retinol binding protein and is produced almost exclusively in the liver. Thus, we believe TTR is a suitable target for an RNAi therapeutic formulated to maximize delivery to liver cells. ALN-TTR targets wild-type and all mutant forms of TTR, including the V30M mutation, and therefore is a potential therapeutic for the treatment of all forms of ATTR, including FAP and FAC.

In December 2009, we filed regulatory applications for ALN-TTR01 and plan to initiate a Phase I trial in ATTR patients in the first half of 2010. ALN-TTR01 is a systemically delivered RNAi therapeutic candidate that employs the first-generation LNP formulation known as SNALP, developed in collaboration with Tekmira. In parallel, we are also advancing ALN-TTR02 utilizing second-generation LNPs.

In pre-clinical studies with hTTR V30M transgenic mice, ALN-TTR treatment led to potent and robust reduction of mutant V30M TTR mRNA levels in the liver and mutant protein levels in the circulation. In non-human primates, administration of ALN-TTR resulted in potent reduction of wild-type TTR. Moreover, durability studies in transgenic mice and non-human primates demonstrated reduction of TTR serum protein and liver mRNA levels for at least three weeks post-administration of ALN-TTR. When administered to hTTR V30M transgenic mice, ALN-TTR blocked the deposition of mutant V30M TTR protein in a number of tissues known to be affected by the disease, including sciatic nerve, sensory ganglion, intestine, esophagus and stomach. These tissues are all sites of TTR deposition in FAP patients, and are locations of amyloid pathology associated with sensory and autonomic neuropathy and severe gastrointestinal dysfunction.

Our findings demonstrate the potential therapeutic benefit of an RNAi therapeutic targeting TTR for the treatment of ATTR. Moreover, siRNA treatment may be superior to liver transplantation based on the ability to simultaneously reduce the expression of mutant, as well as wild-type, TTR. ATTR is also one example of a number of orphan-like indications where there is a very high unmet need and the potential for early biomarker data in clinical studies,

enabling rapid proof-of-concept and a clear opportunity for a large therapeutic impact in patients.

***Hypercholesterolemia***

**Market Opportunity.** Coronary artery disease, or CAD, is the leading cause of mortality in the United States, responsible for 40% of all deaths annually. Hypercholesterolemia, defined as a high level of LDL cholesterol, or LDL-c, in the blood, is one of the major risk factors for CAD. Although current therapies are effective in many patients, studies have shown that as many as 45% of these patients do not achieve adequate control



## **Table of Contents**

of their high cholesterol level with existing treatments, which include drugs known as statins. Currently in the United States, there are almost 500,000 patients with high cholesterol levels not controlled by the use of existing lipid lowering therapies. These patients are said to have refractory or poorly controlled hypercholesterolemia and constitute a potential target population for our product candidate.

**Current Treatments.** The current standard of care for patients with hypercholesterolemia includes the use of several agents. The first treatment often prescribed is a drug from the statin family. Commonly prescribed statins include Lipitor® (atorvastatin), Zocor® (simvastatin), Crestor® (rosuvastatin) and Pravachol® (pravastatin). A different type of drug, such as Zetia® (ezetimibe) and Vytorin® (ezetimibe/simvastatin), which reduces dietary cholesterol uptake from the gut, may also be used either on its own or in combination with a statin. Despite these therapies, there are many patients who have refractory or poorly controlled hypercholesterolemia and require more intensive treatment. In addition, some patients do not tolerate current treatments and at least five percent of those treated with a statin have to stop because of side-effects. In patients with very high uncontrolled cholesterol levels, a procedure called lipid apheresis is used, which effectively removes cholesterol from the blood using a machine specifically designed for this process. However, this procedure is inconvenient and uncomfortable, requiring regular weekly visits to a doctor's office.

**Alnylam Program.** In January 2010, we announced that we expect ALN-PCS, a systemically delivered RNAi therapeutic candidate targeting PCSK9 for the treatment of hypercholesterolemia, to be our next clinical candidate. ALN-PCS is being advanced using second-generation LNPs for systemic delivery.

PCSK9 is a widely acknowledged target for the treatment of hypercholesterolemia by lowering of LDL-c levels. PCSK9 is a protein that is produced by the liver but circulates in the bloodstream. The liver determines cholesterol levels, in part by taking up or absorbing LDL-c from the bloodstream. PCSK9 reduces the liver's capacity to absorb LDL-c. Recent evidence indicates that, if PCSK9 activity could be reduced, the liver should increase its uptake of LDL-c and blood cholesterol levels should decrease. In fact, some individuals have been shown to have a genetic mutation in PCSK9 that lowers its activity and results in increased liver LDL-c uptake and lowered blood cholesterol levels. In turn, these individuals have been shown to have a dramatically reduced risk of CAD, including myocardial infarction or heart attack. In addition, studies have shown that PCSK9 levels are increased by statin therapy while LDL-c levels are decreased, suggesting that the introduction of a PCSK9 inhibitor to statin therapy may result in even further reductions in LDL-c levels.

We began our ALN-PCS program in collaboration with The University of Texas Southwestern Medical Center, or UTSW. As part of the UTSW collaboration, we and UTSW are testing RNAi therapeutic candidates targeting PCSK9 in certain UTSW animal models. Non-human primate data for our ALN-PCS program has demonstrated efficient silencing of PCSK9 and rapid and durable reductions in LDL blood cholesterol levels by greater than 50%.

### ***Huntington's Disease (HD)***

**Market Opportunity.** Huntington's disease, or HD, is a fatal, inherited and progressive brain disease that results in uncontrolled movements, loss of intellectual faculties, emotional disturbance and premature death. HD patients typically first start to develop the disease in their third or fourth decade of life and have an average survival of only 10 to 20 years after initial diagnosis. The disease is associated with the production of an altered form of a protein known as huntingtin, the presence of which is believed to trigger the death of important cells in the brain. This autosomal dominant, neurodegenerative disease afflicts approximately 30,000 patients in the United States. An estimated 150,000 additional people in the United States carry the mutant huntingtin gene and, therefore, have an approximate 50% risk of developing the disease in their lifetimes.

**Current Treatments.** The current treatment of this severe disease is supportive care and symptomatic therapy, with no drugs or therapies available that have been shown to slow the underlying disease progression and the inexorable erosion of the patient's nerve cell functionality.

**Alnylam Program.** In collaboration with Medtronic, we are seeking to develop a novel drug-device product incorporating an RNAi therapeutic candidate targeting the huntingtin gene, delivered using an implantable infusion device, that will protect these cells by suppressing huntingtin mRNA and the disease causing protein. Alnylam scientists and collaborators have published and presented the data from our ALN-HTT program comprised of

## **Table of Contents**

*in vitro*, rodent and non-human primate data demonstrating that the administration of ALN-HTT results in robust silencing of the huntingtin gene and reduced expression of the huntingtin protein, achieves broad distribution following continuous direct central nervous system administration, and is safe and well tolerated in rats and non-human primates at clinically relevant doses.

The ALN-HTT program is part of a 50-50 co-development/profit share relationship with Medtronic for the United States market. Outside the United States, Medtronic will be solely responsible for the development and commercialization of the drug-device.

## **Discovery Programs**

In addition to our development efforts on RSV, liver cancers, ATTR, hypercholesterolemia and HD, we are conducting research activities to discover RNAi therapeutics to treat various diseases. The diseases for which we have discovery programs include: viral hemorrhagic fever, including the Ebola virus, which can cause severe, often fatal infection and poses a potential biological safety risk and bioterrorism threat; Parkinson's disease, a progressive brain disease, which is characterized by uncontrollable tremor, and, in some cases, may result in dementia; and progressive multifocal leukoencephalopathy, or PML, which is a disease of the central nervous system caused by viral infection in immune compromised patients. We are also pursuing other undisclosed internal pre-clinical programs.

In addition to these programs, as part of our collaborations with Novartis, Roche and Takeda, we have research activities to discover RNAi therapeutics directed to a number of undisclosed targets.

## **Our Collaboration and Licensing Strategy**

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

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 partnerships on specific RNAi therapeutic programs. We have entered into broad, non-exclusive platform license agreements with Roche and Takeda, under which we are also collaborating with each of Roche and Takeda on RNAi drug discovery for one or more disease targets. We are pursuing 50-50 co-development programs with Cubist and Medtronic for the development and commercialization of ALN-RSV02 and ALN-HTT, respectively. In addition, we have entered into a product alliance with Kyowa Hakko Kirin for the development and commercialization of ALN-RSV in territories not covered by the Cubist agreement, which include Japan and other markets in Asia. We also have discovery and development alliances with Isis, Novartis and Biogen Idec.

We also seek opportunities to form new ventures in areas outside our core strategic focus. For example, during 2009, we established Alnylam Biotherapeutics, an internal effort regarding the application of RNAi technology to improve the manufacturing processes for biologics, which is comprised of recombinant proteins, monoclonal antibodies and vaccines. This initiative has the potential to create new business opportunities. In addition, during 2007, we formed Regulus, together with Isis, to capitalize on our technology and intellectual property in the field of microRNA-based therapeutics. Given the broad applications for RNAi technology, we believe additional opportunities exist for new ventures.

To generate revenues from our intellectual property rights, we grant licenses to biotechnology companies under our InterfeRx program for the development and commercialization of RNAi therapeutics for specified targets in which we

have no direct strategic interest. We also license key aspects of our intellectual property to companies active in the research products and services market, which includes the manufacture and sale of reagents. Our InterfeRx and research product licenses aim to generate modest near-term revenues that we can re-invest in the development of our proprietary RNAi therapeutics pipeline. As of January 31, 2010, we had granted such licenses, on both an exclusive and non-exclusive basis, to approximately 20 companies.

Since delivery of RNAi therapeutics remains a major objective of our research activities, we also look to form collaboration and licensing agreements with other companies and academic institutions to gain access to delivery

## **Table of Contents**

technologies. For example, we have entered into agreements with Tekmira, MIT, UBC and AICana, among others, to focus on various delivery strategies. We have also entered into license agreements with Isis, Max-Planck-Innovation GmbH, Tekmira and MIT, as well as a number of other entities, to obtain rights to important intellectual property in the field of RNAi. In April 2009, we established a new collaboration with Isis to focus on the development of ssRNAi technology.

Finally, we seek funding for the development of our proprietary RNAi therapeutics pipeline from the government and foundations. In 2006, NIAID awarded us a contract to advance the development of a broad spectrum RNAi anti-viral therapeutic against hemorrhagic fever virus, including the Ebola virus. In 2007, the Defense Threat Reduction Agency, or DTRA, an agency of the United States Department of Defense, awarded us a contract to advance the development of a broad spectrum RNAi anti-viral therapeutic for hemorrhagic fever virus, which contract ended in February 2009. In addition, we have obtained funding for pre-clinical discovery programs from organizations such as The Michael J. Fox Foundation.

### ***Strategic Alliances***

We have formed, and intend to continue to form, strategic alliances to gain access to the financial, technical, clinical and commercial resources necessary to develop and market RNAi therapeutics. We expect these alliances to provide us with financial support in the form of upfront cash payments, license fees, equity investments, research and development funding, milestone payments and/or royalties or profit sharing based on sales of RNAi therapeutics.

### **Platform Alliances.**

**Roche.** In July 2007, we and, for limited purposes, Alnylam Europe AG, or Alnylam Europe, entered into a license and collaboration agreement with Roche. Under the license and collaboration agreement, which became effective in August 2007, 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. The license is initially limited to the therapeutic areas of oncology, respiratory diseases, metabolic diseases and certain liver diseases, and may be expanded to include up to 18 additional therapeutic areas, comprising substantially all other fields of human disease, as identified and agreed upon by the parties, upon payment to us by Roche of an additional \$50.0 million for each additional therapeutic area, if any.

In consideration for the rights granted to Roche under the license and collaboration agreement, Roche paid us \$273.5 million in upfront cash payments. In addition, in exchange for our contributions under the collaboration agreement, for each RNAi therapeutic product developed by Roche, its affiliates or sublicensees under the collaboration agreement, we are entitled to receive milestone payments upon achievement of specified development and sales events, totaling up to an aggregate of \$100.0 million per therapeutic target, together with royalty payments based on worldwide annual net sales, if any. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any milestone or royalty payments from Roche.

Under the license and collaboration agreement, we and Roche also agreed to collaborate on the discovery of RNAi therapeutic products directed to one or more disease targets, subject to our contractual obligations to third parties. In October 2009, we and Roche advanced our alliance to initiate this therapeutic collaboration stage, referred to as the Discovery Collaboration. Under this Discovery Collaboration, we and Roche are collaborating on the discovery and development of specific RNAi therapeutic products and each party contributes key delivery technologies in the effort, which is focused on specific disease targets. We and Roche intend to co-develop and co-commercialize RNAi therapeutic products in the U.S. market and we are eligible to receive additional milestone and royalty payments for products developed in the rest of the world, if any. After a pre-specified period of collaborative activities, each party

will have the option to opt-out of the day-to-day development activities in exchange for reduced milestones and royalty payments in the future. The Discovery Collaboration is governed by the joint steering committee that is comprised of an equal number of representatives from each party.

The term of the license and collaboration agreement generally ends upon the later of ten years from the first commercial sale of a licensed product and the expiration of the last-to-expire patent covering a licensed product. We estimate that our fundamental RNAi patents covered under the license and collaboration agreement will expire both in and outside the United States generally between 2016 and 2025, subject to any potential patent term extensions

**Table of Contents**

and/or supplemental protection certificates extending such term extensions in countries where such extensions may become available. Roche may terminate the license and collaboration agreement, on a licensed product-by-licensed product, licensed patent-by-licensed patent, and country-by-country basis, upon 180-days prior written notice to us, but is required to continue to make milestone and royalty payments to us if any royalties were payable on net sales of a terminated licensed product during the previous 12 months. The license and collaboration agreement may also be terminated by either party in the event the other party fails to cure a material breach under the license and collaboration agreement.

In connection with the execution of the license and collaboration agreement, we executed a common stock purchase agreement with Roche Finance Ltd, or Roche Finance, an affiliate of Roche. Under the terms of the common stock purchase agreement, in August 2007, Roche Finance purchased 1,975,000 shares of our common stock at \$21.50 per share, for an aggregate purchase price of \$42.5 million. Under the terms of the common stock purchase agreement, in the event we propose to sell or issue any of our equity securities, subject to specified exceptions, we agreed to grant to Roche Finance the right to acquire additional securities, such that Roche Finance would be able to maintain its ownership percentage in us. Roche Finance agreed that until August 9, 2010, neither it nor any specified affiliates will acquire any of our securities or assets (other than an acquisition resulting in such entities beneficially owning less than five percent of our total outstanding voting securities), participate in any tender or exchange offer, merger or other business combination involving us or seek to control our management, board of directors or policies, subject to specified exceptions. Roche Finance also agreed that neither it nor any specified affiliates would sell or transfer any of our equity securities during the period prior to August 9, 2009 and that it will limit the volume of such sales or transfers in a single day during the following one-year period, in each case, for so long as Roche Finance and such affiliates beneficially own more than two and one half percent of the total outstanding shares of our common stock.

In connection with the execution of the license and collaboration agreement and the common stock purchase agreement, we also executed a stock purchase agreement with Alnylam Europe and Roche Beteiligungs GmbH, or Roche Germany, an affiliate of Roche. Under the terms of the Alnylam Europe stock purchase agreement, we 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 us all of the issued and outstanding shares of Roche Kulmbach for an aggregate purchase price of \$15.0 million. The Alnylam Europe stock purchase agreement included transition services that were performed by Roche Kulmbach employees at various levels through August 2008. We reimbursed Roche for these services at an agreed-upon rate.

In connection with the license and collaboration agreement and the common stock purchase agreement, during 2007, we paid \$27.5 million in license fees to our licensors, primarily Isis, in accordance with the applicable license agreements with those parties.

**Takeda.** 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 an upfront payment of \$100.0 million. Takeda is also required to make the 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 due upon achievement of specified technology transfer activities, but no later than May 2010, and \$10.0 million of which is due upon achievement of specified technology transfer activities within 24 to 36 months after execution of



## **Table of Contents**

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, if any, comprising substantially all other fields of human disease, as identified and agreed upon by the parties. In addition, for each RNAi therapeutic product developed by Takeda, its affiliates and sublicensees, we are entitled to receive specified development and commercialization milestones, totaling up to \$171.0 million per product, together with royalty payments based on worldwide annual net sales, if any. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any milestone or royalty payments from Takeda.

Pursuant to the Takeda agreement, we and Takeda are also collaborating 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 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-RSV 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, a joint research collaboration committee and a joint delivery collaboration committee, 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. We estimate that our fundamental RNAi patents covered under the Takeda agreement will expire both in and outside the United States generally between 2016 and 2025, subject to any potential patent term extensions and/or supplemental protection certificates extending such term extensions in countries where such extensions may become available. 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, 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.

In connection with the Takeda agreement, during 2008, we paid \$5.0 million of license fees to our licensors, primarily Isis, in accordance with the applicable license agreements with those parties.

## **Discovery and Development Alliances.**

**Isis.** In April 2009, we and Isis amended and restated our existing strategic collaboration and license agreement, originally entered into in March 2004, to extend the broad cross-licensing arrangement regarding double-stranded RNAi that was established in 2004, pursuant to which Isis granted us licenses to its current and future patents and patent applications relating to chemistry and to RNA-targeting mechanisms for the research, development or commercialization of double-stranded RNA, or dsRNA, products. We have the right to use Isis technologies in our development programs or in collaborations and Isis has agreed not to grant licenses under these patents to any other organization for the discovery, development and commercialization of dsRNA products designed to work through an RNAi mechanism, except in the context of a collaboration in which Isis plays an active role. We granted Isis non-exclusive licenses to our current and future patents and patent applications relating to RNA-targeting mechanisms and to chemistry for research use. We also granted Isis the non-exclusive right to develop and commercialize dsRNA products developed using RNAi technology against a limited number of targets. In addition, we granted Isis non-exclusive rights to research, develop and commercialize single-stranded RNA products.

We agreed to pay Isis milestone payments, totaling up to approximately \$3.4 million, upon the occurrence of specified development and regulatory events, and royalties on sales, if any, for each product that we or a collaborator develops using Isis intellectual property. In addition, we agreed to pay to Isis a percentage of specified fees from strategic collaborations we may enter into that include access to Isis intellectual property. Isis agreed to pay us, per therapeutic target, a license fee of \$0.5 million, and milestone payments totaling approximately \$3.4 million, payable upon the occurrence of specified development and regulatory events, and royalties on sales, if any, for each

## Table of Contents

product developed by Isis or a collaborator that utilizes our intellectual property. Isis has the right to elect up to ten non-exclusive target licenses under the agreement and has the right to purchase one additional non-exclusive target per year during the term of the collaboration.

As part of the amended and restated Isis agreement, we and Isis established a new collaborative effort focused on the development of ssRNAi technology. Under the amended and restated Isis agreement, we obtained from Isis a co-exclusive, worldwide license to Isis' current and future patents and patent applications relating to chemistry and RNA-targeting mechanisms to research, develop and commercialize ssRNAi products. Each party has the opportunity to discover and develop drugs employing the ssRNAi technology. Under the terms of the amended and restated Isis agreement, we will potentially pay Isis up to an aggregate of \$31.0 million in license fees, payable in four tranches, that include \$11.0 million paid on signing, \$10.0 million payable in October 2010, or if and when *in vivo* efficacy in rodents is demonstrated if sooner, \$5.0 million upon achievement of *in vivo* efficacy in non-human primates, and \$5.0 million upon initiation of the first clinical trial with an ssRNAi drug, subject to our right to unilaterally terminate the research program. We are funding research activities at a minimum of \$3.0 million each year for three years with research and development activities conducted by both us and Isis. If we develop and commercialize drugs utilizing ssRNAi technology on our own or with a partner, we would be required to make milestone payments to Isis, totaling up to \$18.5 million per product, as well as royalties. Also, Isis initially is eligible to receive up to 50% of any sublicense payments due to us from a third party based on our partnering of ssRNAi products, which amount will decline over time as our investment in the technology and drugs increases. In turn, we are eligible to receive up to five percent of any sublicense payments due to Isis from a third party based on Isis' partnering of ssRNAi products.

We have the unilateral right to terminate the ssRNAi research program before September 30, 2010, in which event any licenses to ssRNAi products granted by Isis to us under the amended and restated Isis agreement, and any obligation thereunder by us to pay milestone payments, royalties or sublicense payments to Isis for such ssRNAi products, would also terminate.

The term of the Isis agreement generally ends upon the expiration of the last-to-expire patent licensed thereunder, whether such patent is a patent licensed by us to Isis, or vice versa. As the license will include additional patents, if any, filed to cover future inventions, if any, the date of expiration cannot be determined at this time.

**Novartis.** Beginning in September 2005, we entered into a series of transactions with Novartis which we refer to as our broad Novartis alliance. At that time, we and Novartis executed a stock purchase agreement and an investor rights agreement. When the transactions contemplated by the stock purchase agreement closed in October 2005, the investor rights agreement became effective and we and Novartis executed a research collaboration and license agreement. The collaboration and license agreement had an initial term of three years, with an option for two additional one-year extensions at the election of Novartis. In July 2009, Novartis elected to further extend the term for the fifth and final planned year, through October 2010.

Under the terms of the collaboration and license agreement, we and Novartis 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. In consideration for rights granted to Novartis under the collaboration and license agreement, Novartis made an upfront payment of \$10.0 million to us in October 2005, partly to reimburse prior costs incurred by us to develop *in vivo* RNAi technology. The collaboration and license agreement also includes terms under which Novartis has been providing us with research funding and development milestone payments, and may provide us in the future with sales milestone payments as well as royalties on annual net sales of products resulting from the collaboration, if any. The amount of research funding provided by Novartis under the collaboration and license agreement during the research term is dependent upon the number of active programs on which we are collaborating with them at any given time and the number of our employees that are working on those programs, in respect of which Novartis reimburses us at an agreed upon rate. Under the terms of the collaboration and license agreement, Novartis has the right to select up to 30

exclusive targets to include in the collaboration, which number may be increased to 40 under certain circumstances and upon additional payments. For RNAi therapeutic products developed under the agreement, if any, we would be entitled to receive milestone payments upon achievement of certain specified development and annual net sales events, up to an aggregate of \$75.0 million per therapeutic product. Due to the uncertainty of pharmaceutical development and the high historical

**Table of Contents**

failure rates generally associated with drug development, we may not receive any additional milestone payments or any royalty payments from Novartis.

Under the terms of the collaboration and license agreement, we retain the right to discover, develop, commercialize and manufacture compounds that function through the mechanism of RNAi, or products that contain such compounds as an active ingredient, with respect to targets not selected by Novartis for inclusion in the collaboration, provided that Novartis has a right of first offer with respect to an exclusive license for additional targets before we partner any of those additional targets with third parties.

The collaboration and license agreement also provides Novartis with a non-exclusive option to integrate into its operations our intellectual property relating to RNAi technology, excluding any technology related to delivery of nucleic acid based molecules. Novartis may exercise this integration option at any point during the research term, which term is currently expected to expire in the fourth quarter of 2010. In connection with the exercise of the integration option, Novartis would be required to make additional payments to us totaling \$100.0 million, payable in full at the time of exercise, which payments would include an option exercise fee, a milestone based on the overall success of the collaboration, and pre-paid milestones and royalties that could become due as a result of future development of products using our technology. This amount would be offset by any license fees due to our licensors in accordance with the applicable license agreements with those parties. In addition, under this license grant, Novartis may be required to make milestone and royalty payments to us in connection with the development and commercialization of RNAi therapeutic products, if any. The license grant under the integration option, if exercised by Novartis, would be structured similarly to our non-exclusive platform licenses with Roche and Takeda.

Novartis may terminate the collaboration and license agreement in the event that we materially breach our obligations. We may terminate the agreement with respect to particular programs, products and/or countries in the event of specified material breaches by Novartis of its obligations, or in its entirety under specified circumstances for multiple such breaches.

Under the terms of the stock purchase agreement, in October 2005, Novartis purchased 5,267,865 shares of our 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 our outstanding common stock as of the date of issuance. In addition, under the investor rights agreement, we granted Novartis rights to acquire additional equity securities in the event that we propose to sell or issue any equity securities, subject to specified exceptions, as described in the investor rights agreement, such that Novartis would be able to maintain its then-current ownership percentage in our outstanding common stock. Pursuant to terms of the investor rights agreement, in May 2008, Novartis purchased 213,888 shares of our common stock at a purchase price of \$25.29 per share resulting in a payment to us of \$5.4 million. In May 2009, Novartis purchased 65,922 shares of our common stock at a purchase price of \$17.50 per share, resulting in an aggregate payment to us of \$1.2 million. This purchase allowed Novartis to maintain its ownership position of 13.4% of our outstanding common stock. The exercises of this right did not result in any changes to existing rights or any additional rights to Novartis. Further, during the term described in the investor rights agreement, Novartis is permitted to own no more than 19.9% of our outstanding shares. At December 31, 2009, Novartis owned 13.3% of our outstanding common stock.

Under the terms of the investor rights agreement, we also granted Novartis demand and piggyback registration rights under the Securities Act of 1933 for the shares of our common stock held by Novartis. Novartis agreed, until the later of (1) October 12, 2008 and (2) the date of termination or expiration of the selection term, which is currently expected to occur in 2010, not to acquire any of our securities, other than an acquisition resulting in Novartis and its affiliates beneficially owning less than 20% of our total outstanding voting securities, participate in any tender or exchange offer, merger or other business combination involving us or seek to control or influence our management, board of directors or policies, subject to specified exceptions described in the investor rights agreement.

In addition to the broad Novartis alliance, in February 2006, we entered into the Novartis flu alliance. Under the terms of the Novartis flu alliance, we and Novartis had joint responsibility for the development of RNAi therapeutics for pandemic flu. This program was stopped during 2008 and currently there are no specific resource commitments for this program.

## **Table of Contents**

**Biogen Idec.** In September 2006, we entered into a collaboration and license agreement with Biogen Idec. The collaboration is focused on the discovery and development of therapeutics based on RNAi for the potential treatment of PML. Under the terms of the Biogen Idec agreement, we granted Biogen Idec an exclusive license to distribute, market and sell certain RNAi therapeutics to treat PML and Biogen Idec has agreed to fund all related research and development activities. We received an upfront \$5.0 million payment from Biogen Idec. In addition, upon the successful development and utilization of a product resulting from the collaboration, if any, Biogen Idec would be required to pay us milestone payments, totaling \$51.0 million, and royalty payments on sales, if any. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any milestone or royalty payments from Biogen Idec. The pace and scope of future development of this program is the responsibility of Biogen Idec. We expect to expend limited resources on this program in 2010.

Unless earlier terminated, the Biogen Idec agreement will remain in effect until the expiration of all payment obligations under the agreement. Either we or Biogen Idec may terminate the agreement in the event that the other party breaches its obligations thereunder. Biogen Idec may also terminate the agreement, on a country-by-country basis, without cause upon 90 days prior written notice.

## **Product Alliances.**

**Medtronic.** In July 2007, we entered into an amended and restated collaboration agreement with Medtronic to pursue the development of therapeutic products for the treatment of neurodegenerative disorders. The amended and restated collaboration agreement supersedes the collaboration agreement entered into by the parties in February 2005, and continues the existing collaboration between the parties focusing on the delivery of RNAi therapeutics to specific areas of the brain using implantable infusion systems.

Under the terms of the amended and restated collaboration agreement, we and Medtronic are continuing our existing development program focused on developing a combination drug-device product for the treatment of Huntington's disease. In addition, we and Medtronic may jointly agree to collaborate on additional product development programs for the treatment of other neurodegenerative diseases, which can be addressed by the delivery of siRNAs discovered and developed using our RNAi therapeutics platform to the human nervous system through implantable infusion devices developed by Medtronic. We are responsible for supplying the siRNA component and Medtronic is responsible for supplying the device component of any product resulting from the collaboration.

With respect to the initial product development program focused on Huntington's disease, each party is funding 50% of the development efforts for the United States while Medtronic is responsible for funding development efforts outside the United States. Medtronic will commercialize any resulting products and pay royalties to us based on net sales of such products, if any, which royalties in the United States are designed to approximate 50% of the profit associated with the sale of such product and which royalties in Europe are similar to more traditional pharmaceutical royalties, in that they are intended to reflect each party's contribution.

Each party has the right to opt-out of its obligation to fund the program under the agreement at certain stages, and the agreement provides for revised economics based on the timing of any such opt-out. Other than pursuant to the initial product development program, and subject to specified exceptions, neither party may research, develop, manufacture or commercialize products that use implanted infusion devices for the direct delivery of siRNAs to the human nervous system to treat Huntington's disease during the term of such program.

The amended and restated collaboration agreement expires, on a product-by-product and country-by-country basis, upon expiration of the royalty term for the applicable product. The royalty term is the longer of a specified number of years from the first commercial sale of the applicable product and the expiration of the last-to-expire of specified

patent rights. Royalties are paid at a lower level during any part of a royalty term in which specified patent coverage does not exist. Either party may terminate the amended and restated collaboration agreement on 60 days prior written notice if the other party materially breaches the agreement in specified ways and fails to cure the breach within the 60-day notice period. Either party may also terminate the agreement in the event that specified pre-clinical testing does not yield results meeting specified success criteria.



**Table of Contents**

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

Under the terms of the Kyowa Hakko Kirin agreement, in June 2008, Kyowa Hakko Kirin paid us an upfront cash payment of \$15.0 million. In addition, Kyowa Hakko Kirin is required to make payments to us upon achievement of specified development and sales milestones totaling up to \$78.0 million, and royalty payments based on annual net sales, if any, of RNAi therapeutics for RSV by Kyowa Hakko Kirin, its affiliates and sublicensees in the licensed territory. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any milestone or royalty payments from Kyowa Hakko Kirin.

Our collaboration with Kyowa Hakko Kirin is governed by a joint steering committee that is comprised of an equal number of representatives from each party. Under the agreement, Kyowa Hakko Kirin is establishing a development plan for the ALN-RSV program relating to the development activities to be undertaken in the licensed territory, with the initial focus on Japan. Kyowa Hakko Kirin is responsible, at its expense, for all development activities under the development plan that are reasonably necessary for the regulatory approval and commercialization of an RNAi therapeutic for the treatment of RSV in Japan and the rest of the licensed territory. We are responsible for supply of the product to Kyowa Hakko Kirin under a supply agreement unless Kyowa Hakko Kirin 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 term of the Kyowa Hakko Kirin agreement generally ends on a country-by-country basis upon the later of (1) the expiration of our last-to-expire patent covering a licensed product and (2) the tenth anniversary of the first commercial sale in the country of sale. We estimate that our principal patents covered under the Kyowa Hakko Kirin agreement will expire both in and outside the United States generally between 2016 and 2025. These patent rights are subject to any potential patent term extensions and/or supplemental protection certificates extending such term extensions in countries where such extensions may become available. Additional patent filings relating to the collaboration may be made in the future. The Kyowa Hakko Kirin 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 Kirin may terminate the agreement without cause upon 180-days prior written notice to us, subject to certain conditions.

**Cubist.** In January 2009, we entered into a license and collaboration agreement with Cubist to develop and commercialize therapeutic products based on certain of our RNAi technology for the treatment of RSV. Licensed products initially included ALN-RSV01, as well as several other second-generation RNAi-based RSV inhibitors. In November 2009, we and Cubist entered into an amendment to our license and collaboration agreement, which provides that we and Cubist will focus our collaboration and joint development efforts on ALN-RSV02, a second-generation compound, intended for use in pediatric patients. Consistent with the original license and collaboration agreement, we and Cubist each bears one-half of the related development costs for ALN-RSV02. Pursuant to the terms of the amendment, we are also continuing to develop ALN-RSV01 for adult transplant patients at our sole discretion and expense. Cubist has the right to resume the collaboration on ALN-RSV01 in the future, which right may be exercised for a specified period of time following the completion of our Phase IIb trial of ALN-RSV01 in adult lung transplant patients infected with RSV, subject to the payment by Cubist of an opt-in fee representing reimbursement of an agreed upon percentage of certain of our development expenses for ALN-RSV01.

Under the terms of the Cubist agreement, we and Cubist share responsibility for developing licensed products in North America and each bears one-half of the related development costs, subject to the terms of the November 2009 amendment. Our collaboration with Cubist for the development of licensed products in North America is governed by a joint steering committee comprised of an equal number of representatives from each party. Cubist will have the sole right to commercialize licensed products in North America with costs associated with such activities and any resulting profits or losses to be split equally between us and Cubist. Throughout the rest of the

## **Table of Contents**

world, referred to as the Royalty Territory, excluding Asia, where we have previously partnered our ALN-RSV program with Kyowa Hakko Kirin, Cubist has an exclusive, royalty-bearing license to develop and commercialize licensed products.

In consideration for the rights granted to Cubist under the agreement, in January 2009, Cubist paid us an upfront cash payment of \$20.0 million. Cubist also has an obligation under the agreement to pay us milestone payments, totaling up to an aggregate of \$82.5 million, upon the achievement of specified development and sales events in the Royalty Territory. In addition, if licensed products are successfully developed, Cubist will be required to pay us double digit royalties on net sales of licensed products in the Royalty Territory, if any, subject to offsets under certain circumstances. Upon achievement of certain development milestones, we will have the right to convert the North American co-development and profit sharing arrangement into a royalty-bearing license and, in addition to royalties on net sales in North America, will be entitled to receive additional milestone payments totaling up to an aggregate of \$130.0 million upon achievement of specified development and sales events in North America, subject to the timing of the conversion by us and the regulatory status of a licensed product at the time of conversion. If we make the conversion to a royalty-bearing license with respect to North America, then North America becomes part of the Royalty Territory. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any milestone or royalty payments from Cubist.

Unless terminated earlier in accordance with the agreement, the agreement expires on a country-by-country and licensed product-by-licensed product basis, (a) with respect to the Royalty Territory, upon the latest to occur of (1) the expiration of the last-to-expire Alnylam patent covering a licensed product, (2) the expiration of the Regulatory-Based Exclusivity Period (as defined in the Cubist agreement) and (3) ten years from first commercial sale in such country of such licensed product by Cubist or its affiliates or sublicensees, and (b) with respect to North America, if we have not converted North America into the Royalty Territory, upon the termination of the agreement by Cubist upon specified prior written notice. We estimate that our fundamental RNAi patents covered under the Cubist agreement will expire both in and outside of the United States generally between 2016 and 2025. Certain claims covering ALN-RSV compounds in the United States would expire in 2026. These patent rights are subject to any potential patent term extensions and/or supplemental protection certificates extending such term extensions in countries where such extensions may become available. In addition, more patent filings relating to the collaboration may be made in the future. Cubist has the right to terminate the agreement at any time (1) upon three months prior written notice if such notice is given prior to the acceptance for filing of the first application for regulatory approval of a licensed product or (2) upon nine months prior written notice if such notice is given after the acceptance for filing of the first application for regulatory approval. Either party may terminate the agreement in the event the other party fails to cure a material breach or upon patent-related challenges by the other party.

During the term of the Cubist agreement, neither party nor its affiliates may develop, manufacture or commercialize anywhere in the world, outside of Asia, a therapeutic or prophylactic product that specifically targets RSV, except for licensed products developed, manufactured or commercialized pursuant to the agreement.

### ***microRNAi-based Therapeutics***

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

Regulus, which initially was established as a limited liability company, converted to a C corporation as of January 2, 2009 and changed its name to Regulus Therapeutics Inc. In consideration for our and Isis initial interests in Regulus, we and Isis each granted Regulus exclusive licenses to our intellectual property for certain microRNA-based therapeutics as well as certain patents in the microRNA field. In addition, we made an initial cash contribution to

Regulus of \$10.0 million, resulting in us and Isis making initial capital contributions to Regulus of approximately equal aggregate value. In March 2009, we and Isis each purchased \$10.0 million of Series A preferred stock of Regulus. We and Isis currently own approximately 49% and 51%, respectively, of Regulus and there are currently no other third party investors in Regulus. Regulus continues to operate as an independent company with a separate board of directors, scientific advisory board and management team, some of whom have options to purchase

**Table of Contents**

common stock of Regulus. Members of the board of directors of Regulus who are our employees or Isis employees are not eligible to receive options to purchase Regulus common stock.

Regulus is exploring therapeutic opportunities that arise from alterations in microRNA expression. Since microRNAs are believed to regulate the expression of broad networks of genes and biological pathways, microRNA-based therapeutics define a new and potentially high-impact strategy to target multiple points on disease pathways. Conventional messenger RNAs are genetically encoded and in turn instruct the creation of proteins through the process of translation. However, these small microRNAs do not instruct creation of proteins but instead regulate the expression of other genes. There are approximately 700 microRNAs that have been identified in the human genome, and these are believed to regulate the expression of up to 30% of all human genes. Since microRNAs may act as master regulators for physiological pathways or genetic networks to achieve integrated biological functions, affecting the expression of multiple genes in the pathway of disease, microRNAs potentially represent an exciting new platform for drug discovery and development.

To date, microRNAs have been implicated in several disease areas such as cancer, viral infection, inflammatory diseases and metabolic disorders. Regulus most advanced program, which is in pre-clinical research, is a microRNA-based therapeutic candidate that targets miR-122. miR-122 is a liver-expressed microRNA that has been shown to be a critical endogenous host factor for the replication of HCV, and anti-miRs targeting miR-122 have been shown to block HCV infection. HCV infection is a significant disease worldwide, for which emerging therapies target viral genes and, therefore, are prone to viral resistance. Regulus is also pursuing a program that targets miR-21. Pre-clinical studies by Regulus and collaborators have shown that miR-21 is implicated in several therapeutic areas, including heart failure and fibrosis. In addition to these programs, Regulus is also actively exploring additional areas for development of microRNA-based therapeutics, including cancer, other viral diseases, metabolic disorders and inflammatory diseases.

In April 2008, Regulus entered into a worldwide strategic alliance with 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 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 common stock under certain specified circumstances. Regulus 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, if any. In May 2009, Regulus achieved the first demonstration of a pharmacological effect in immune cells by specific microRNA inhibition, the initial discovery milestone under the GSK alliance, which triggered a payment under the agreement.

In February 2010, Regulus and GSK established a new collaboration to develop and commercialize microRNA-based therapeutics targeting miR-122 in all fields, with HCV infection as the lead indication. This new collaboration includes the potential for Regulus to earn more than \$150.0 million in upfront and milestone payments, in addition to royalties, on worldwide sales of products, if any, as Regulus and GSK advance microRNA-based therapeutics targeting miR-122.

We, Isis and Regulus have also entered into a license and collaboration agreement to pursue the discovery, development and commercialization of therapeutic products directed to microRNAs. Under the terms of the license and collaboration agreement, we and Isis assigned to Regulus specified patents and contracts covering microRNA-specific technology. In addition, each of us granted to Regulus an exclusive, worldwide license under our rights to other microRNA-related patents and know-how to develop and commercialize therapeutic products containing compounds that are designed to interfere with or inhibit a particular microRNA, subject to our and Isis existing contractual obligations to third parties. Regulus also has the right to request a license from us and Isis to

develop and commercialize therapeutic products directed to other microRNA compounds, which license is subject to our and Isis approval and to each such party's existing contractual obligations to third parties. Regulus granted to us and Isis an exclusive license to technology developed or acquired by Regulus for use solely within our respective fields (as defined in the license and collaboration agreement), but specifically excluding the right to develop, manufacture or commercialize the therapeutic products for which we and Isis granted rights to Regulus.

## **Table of Contents**

After a sufficient portfolio of data is obtained with respect to each microRNA therapeutic candidate developed by Regulus, Regulus may elect to continue to pursue the development and commercialization of products directed to such microRNA compound and related microRNA compounds, in which event Regulus would be obligated to pay us and Isis a royalty on net sales of any such resulting products. If Regulus decides not to continue to pursue the development and commercialization of products directed to particular microRNA compounds, either we or Isis may pursue development and commercialization of such Regulus products. Development and commercialization of such products by either party would be subject to the payment to Regulus of a specified upfront fee, milestone payments upon achievement of specified regulatory events, royalties on net sales and a portion of income received from sublicensing rights.

In addition, we are also a party to a services agreement with Isis and Regulus. Under the terms of the services agreement, we and Isis provide to Regulus certain research and development and general and administrative services, as set forth in an operating plan mutually agreed upon by us and Isis. Pursuant to this agreement, we and Isis are paid by Regulus for these services.

### ***Alnylam Biotherapeutics***

During 2009, we presented new data regarding the application of RNAi technology to improve the manufacturing processes for biologics, which is comprised of recombinant proteins, monoclonal antibodies and vaccines. This initiative, which we are advancing in an internal effort referred to as Alnylam Biotherapeutics, has the potential to create new business opportunities. In particular, we are advancing RNAi technologies to improve the quantity and quality of biologics manufacturing processes using mammalian cell culture, such as CHO cells. This RNAi technology potentially could be applied to the improvement of manufacturing processes for existing marketed drugs, new drugs in development and for the emerging biosimilars market. We have developed proprietary delivery lipids that enable the efficient transfection of siRNAs into CHO cells when grown in suspension culture. Studies have demonstrated that silencing certain target genes involved in certain CHO cell apoptotic and metabolic pathways resulted in 40% to 60% improved cell viability as compared with untreated cells. As Alnylam Biotherapeutics advances the technology, it plans to seek partnerships with established biologic manufacturers, selling licenses, products and services.

### ***Other RNAi Areas of Opportunity***

We continue to seek additional opportunities to form new ventures in areas outside our core strategic interest. During 2008, we further 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-based 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 the treatment of certain genetic diseases and cancer. We have entered into exclusive license agreements with UTSW, the 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.

We are also evaluating various other opportunities in the areas of stem cell research, genomics, vaccines and other non-coding RNAs. Given the broad applications for RNAi technology, we believe additional opportunities exist for new ventures.

### ***Licenses***

To further enable the field and monetize our intellectual property rights, we have established our InterfeRx program and our research reagents and services licensing program.

**InterfeRx Program.** Our InterfeRx program consists of the licensing of our intellectual property to others for the development and commercialization of RNAi therapeutic products relating to specific targets outside our direct strategic focus. We expect to receive license fees, annual maintenance fees, milestone payments and royalties on sales of any resulting RNAi therapeutic products. Generally, we do not expect to collaborate with our InterfeRx licensees in the development of RNAi therapeutic products, but may do so in certain circumstances. To date, we



## **Table of Contents**

have granted InterfeRx licenses to a number of companies, including GeneCare Research Institute Co., Ltd., or GeneCare, Quark Biotech, Inc., or Quark, Calando Pharmaceuticals, Inc., or Calando, and Tekmira. In general, these licenses allow the licensees to discover, develop and commercialize RNAi therapeutics for a limited number of targets in return for upfront, milestone, license maintenance and/or royalty payments to us. In some cases, we also retained a right to negotiate the ability to co-promote and/or co-commercialize the licensed product, and in one case, we included the rights to discover, develop and commercialize RNAi therapeutics utilizing expressed RNAi (i.e., RNAi mediated by siRNAs generated from DNA constructs introduced into cells). In addition, Benitec Ltd., or Benitec, has an option to take an InterfeRx license, subject to certain conditions. We have granted InterfeRx licenses or options relating to approximately 20 gene targets and, as of January 31, 2010, only eight targets have been selected by InterfeRx partners.

**Research Reagents and Services.** We have granted approximately 15 licenses to our intellectual property for the development and commercialization of research reagents and services, and intend to enter into additional licenses on an ongoing basis. Our target licensees are vendors that provide siRNAs and related products and services for use in biological research. We offer these licenses in return for an initial license fee, annual renewal fees and royalties from sales of siRNA research reagents and services. No single research reagent or research services license is material to our business.

## ***Delivery Initiatives***

We are working internally and with third-party collaborators to extend our capabilities in developing technology to achieve effective and safe delivery of RNAi therapeutics to a broad spectrum of organ and tissue types. In connection with these efforts, we have entered into a number of agreements to evaluate and gain access to certain delivery technologies. In some instances, we are also providing funding to support the advancement of these delivery technologies. Over the past 12 to 18 months, we believe we have made major advances relating to the delivery of RNAi therapeutics, which we describe in more detail below.

In May 2007, we entered into an agreement with the David H. Koch Institute for Integrative Cancer Research at MIT, under which we are sponsoring an exclusive five-year research program focused on the delivery of RNAi therapeutics. In December 2009, we and MIT announced the publication of new data in the journal *PNAS* describing further advancements in the discovery and development of LNPs based on novel lipidoid formulations for the systemic delivery of RNAi therapeutics. Lipidoids are lipid-like materials discovered for the delivery of RNAi therapeutics, and were originally described by us and our collaborators at MIT. In particular, the new research findings demonstrated the discovery, using a combinatorial chemistry-based approach, of new lipidoid materials that facilitate significantly improved *in vivo* potency for RNAi therapeutics. In *in vivo* studies, second generation LNPs employing novel lipidoids showed gene silencing of the clinically relevant gene, TTR, at doses as low as 0.03 mg/kg in non-human primates. Lipidoid formulations represent one of several approaches we are pursuing for systemic delivery of RNAi therapeutics.

In addition, during 2007, we obtained an exclusive worldwide license to the liposomal delivery formulation technology of Tekmira for the discovery, development and commercialization of LNP formulations for the delivery of RNAi therapeutics, and a non-exclusive worldwide license to certain liposomal delivery formulation technology of Protiva Biotherapeutics Inc., or Protiva, for the discovery, development and commercialization of certain LNP formulations for the delivery of RNAi therapeutics. In May 2008, Tekmira acquired 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 these agreements, 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 for RNAi, which we believe are critical for the use of LNP delivery technology. In July 2009, we and Tekmira agreed to jointly participate in a new research collaboration with scientists at UBC and AICana focused on the discovery of novel lipids for use in LNPs for the systemic delivery

of RNAi therapeutics. We are funding the collaborative research over a two-year period, and the work is being conducted by our scientists together with scientists at UBC and AlCana. We will receive exclusive rights to all new inventions as well as sole rights to sublicense any resulting intellectual property to our current and future collaborators. Tekmira will receive rights to use new inventions for their own RNAi therapeutic programs that are licensed under our InterfeRx program.

## **Table of Contents**

In January 2010, we announced the publication of new data in the journal *Nature Biotechnology* from our collaboration with Tekmira and scientists at UBC and AICana. This new study employed a rational design approach for the discovery of novel lipids that can be incorporated into LNPs for systemic delivery of RNAi therapeutics. This research complements the combinatorial chemistry-based approach described above under our MIT collaboration and demonstrates the advantages of using multiple parallel approaches for optimizing LNPs. We have discovered novel lipids based on a medicinal chemistry effort exploring the structure-activity relationships in a lipid which has been used in certain first generation LNPs such as Tekmira's SNALP formulations. *In vivo* data with these new LNPs showed that gene silencing in rodents was achieved following a single injection at doses as low as 0.01 mg/kg and that potent and selective silencing of the clinically relevant gene, TTR, was achieved at doses as low as 0.1 mg/kg in non-human primates. We expect that the significantly improved potency of these second generation LNPs will yield important advantages for advancement of RNAi therapeutics including potentially lowered material requirements, improved therapeutic index and expanded scope of delivery beyond the liver. Alnylam has exclusive rights to the novel lipids described in this work and sole rights to sublicense related intellectual property to its current and future collaborators. Tekmira has rights to use these new inventions for their own RNAi therapeutic programs that are licensed under our InterfeRx program.

As noted above, we are developing ALN-VSP, a systemically delivered RNAi therapeutic candidate, for the treatment of primary and secondary liver cancer. ALN-VSP contains two siRNAs formulated using the first generation LNP formulation known as SNALP, developed in collaboration with Tekmira. We also have rights to use SNALP technology in the advancement of our other systemically delivered RNAi therapeutic programs, and are advancing ALN-TTR01, for the treatment of ATTR, utilizing a first generation SNALP formulation. In parallel with ALN-TTR01, we are advancing ALN-TTR02 utilizing second-generation LNPs. In addition, we have published pre-clinical results from development programs for other systemically delivered RNAi therapeutic candidates, including ALN-PCS, for the treatment of hypercholesterolemia, which we recently identified as our next clinical candidate. ALN-PCS is being advanced using second-generation LNPs for systemic delivery.

In addition to the advances described above, in January 2010, we reported the discovery of a key mechanism related to the systemic delivery of RNAi therapeutics using LNPs. This pre-clinical research was performed in collaboration with scientists at the Max Planck Institute of Molecular Cell Biology and Genetics. The new data document a key mechanism for endogenous targeting of certain LNPs to the liver, provide alternative targeting strategies for the delivery of RNAi therapeutics to the liver, and highlight potential targeting approaches for delivery to non-liver tissues and cell types. Specifically, these *in vitro* and *in vivo* research findings establish the role of ApoE as an endogenous targeting ligand for neutrally charged ionizable LNPs, or iLNPs, but not certain cationic LNPs, or cLNPs, and demonstrate an alternative targeting strategy for the delivery of RNAi therapeutics to the liver using the carbohydrate N-acetylgalactosamine, or GalNAc, as an exogenous ligand.

We are pursuing additional approaches for delivery that include other LNP formulations, mimetic lipoprotein particles, or MLPs, siRNA conjugation strategies and ssRNAi, among others. In addition, we have other RNAi therapeutic delivery collaborations and intend to continue to collaborate with government, academic and corporate third parties to evaluate and gain access to different delivery technologies.

## ***Government Funding***

**NIH.** In September 2006, the NIAID, a component of NIH, 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. As a result of the continued progress of this program, the NIAID appropriated the entire \$23.0 million over the four-year term of the contract, which will be completed in September 2010.

**Department of Defense.** In August 2007, DTRA awarded us a contract to advance the development of a broad spectrum RNAi anti-viral therapeutic for hemorrhagic fever virus. The government initially committed to pay us up to \$10.9 million through February 2009, which included a six-month extension granted by DTRA in July 2008. Following a program review in early 2009, we and DTRA determined not to continue this program and accordingly, the remaining funds of up to \$27.7 million were not accessed.

**Table of Contents****Patents and Proprietary Rights**

We have devoted considerable effort and resources to establish what we believe to be a strong intellectual property position relevant to RNAi therapeutic products and delivery technologies. In this regard, we have amassed a portfolio of patents, patent applications and other intellectual property covering:

fundamental aspects of the structure and uses of siRNAs, including their use as therapeutics, and RNAi-related mechanisms;

chemical modifications to siRNAs that improve their suitability for therapeutic uses;

siRNAs directed to specific targets as treatments for particular diseases;

delivery technologies, such as in the field of cationic liposomes; and

all aspects of our specific development candidates.

We believe that no other company possesses a portfolio of such broad and exclusive rights to the patents and patent applications required for the commercialization of RNAi therapeutics. Our intellectual property estate for RNAi therapeutics includes over 1,800 active cases and over 700 granted or issued patents, of which over 300 are issued or granted in the United States, the European Union, or EU, and Japan. Given the importance of our intellectual property portfolio to our business operations, we intend to vigorously enforce our rights and defend against challenges that have arisen or may arise in this area.

***Intellectual Property Related to Fundamental Aspects and Uses of siRNA and RNAi-related Mechanisms***

In this category, we include United States and foreign patents and patent applications that claim key aspects of siRNA architecture and RNAi-related mechanisms. Specifically included are patents and patent applications covering targeted cleavage of mRNA directed by RNA-like oligonucleotides, dsRNAs of particular lengths and particular structural features, such as blunt and/or overhanging ends. Our strategy has been to secure exclusive rights where possible and appropriate to key patents and patent applications that we believe cover fundamental aspects of RNAi. The following table lists patents and/or patent applications to which we have secured rights that we regard as being fundamental for the use of siRNAs as therapeutics.

<b>Patent Licensors/Owner</b>	<b>Subject Matter</b>	<b>First Priority Date</b>	<b>Inventors</b>	<b>Status</b>	<b>Expiration Date*</b>	<b>Alnylam Rights</b>
Isis	Inactivation of target mRNA	6/6/1996 and 6/6/1997	S. Crooke	U.S. 5,898,031, U.S. 6,107,094, U.S. 7,432,250 & USSN 10/078,949 (allowed) EP 0928290	06/06/2016  06/06/2017	Exclusive rights for therapeutic purposes related to siRNAs**

				Additional applications pending in the U.S. and several foreign jurisdictions		
Carnegie Institution of Washington	Double-stranded RNAs to induce RNAi	12/23/1997	A. Fire, C. Mello	U.S. 6,506,559, U.S. 7,560,438 & U.S. 7,538,095	12/18/2018	Non-exclusive rights for therapeutic purposes
				Additional applications pending in the U.S. and several foreign jurisdictions		
Medical College of Georgia Research Institute, Inc.	Methods for inhibiting gene expression using double-stranded RNA	1/28/1999	Y. Li, M. Farrell, M. Kirby	AU 776150 (Australia) Additional applications pending in the U.S., Europe and Canada	1/28/2020	Exclusive rights

**Table of Contents**

<b>Patent Licensor/Owner</b>	<b>Subject Matter</b>	<b>First Priority Date</b>	<b>Inventors</b>	<b>Status</b>	<b>Expiration Date*</b>	<b>Alnylam Rights</b>
Alnylam	Small double-stranded RNAs as therapeutic products	1/30/1999	R. Kreutzer, S. Limmer	EP 1214945 (revoked/under appeal), EP 1550719 (granted/opposed), EP 1352061 (maintained/under appeal) & EP App. No. 02702247.4 (Intent to Grant), CA 2359180 (Canada), AU 778474 (Australia), ZA 2001/5909 (South Africa), DE 20023125 U1, DE 10066235 & DE 10080167 (Germany) Additional applications pending in the U.S. and several foreign jurisdictions	01/29/2020	Owned
Alnylam	Composition and methods for inhibiting a target nucleic acid with double-stranded RNA	4/21/1999	C. Pachuk, C. Satishchandran	AU 781598 (Australia) Additional applications pending in the U.S. and several foreign jurisdictions	4/19/2020	Owned
Cancer Research Technology Limited	RNAi uses in mammalian oocytes, preimplantation embryos and somatic cells	11/19/1999	M. Zernicka-Goetz, M.J. Evans, D.M. Glover	EP 1230375 (revoked/under appeal), SG 89569 (Singapore), AU 774285 (Australia) Additional applications pending in the U.S. and several foreign jurisdictions	11/17/2020	Exclusive rights for therapeutic purposes
		3/30/2000			03/30/2020	

Edgar Filing: ALNYLAM PHARMACEUTICALS, INC. - Form 10-K

Massachusetts Institute of Technology, Whitehead Institute, Max Planck Gesellschaft***	Mediation of RNAi by small RNAs 21-23 base pairs long		D.P. Bartel, P.A. Sharp, T. Tuschl, P.D. Zamore	EP 1309726, AU 2001249622 (Australia) Additional applications pending in the U.S. and several foreign jurisdictions		Non-exclusive rights for therapeutic purposes***
Max Planck Gesellschaft	Synthetic and chemically modified siRNAs as therapeutic products	12/01/2000, 04/24/2004 and 04/27/2004	T. Tuschl, S. Elbashir, W. Lendeckel	U.S. 7,056,704 & U.S. 7,078,196, EP 1407044, AU 2002235744 (Australia), ZA 2003/3929 (South Africa), SG 96891 (Singapore), NZ 52588 (New Zealand), JP 4 095 895 (Japan), RU 2322500 (Russia), CN 1568373 (China) Additional applications pending in the U.S. and several foreign jurisdictions	11/29/2021	Exclusive rights for therapeutic purposes
Alnylam	Methods for inhibiting a target nucleic acid via the introduction of a vector encoding a double-stranded RNA	1/31/2001	T. Giordano, C. Pachuk, C. Satishchandran	AU 785395 (Australia) Additional applications pending in the U.S., Australia and Canada	1/31/2021	Owned
Cold Spring Harbor Laboratory	RNAi uses in mammalian cells	3/16/2001	D. Beach, G. Hannon	Pending in the U.S. and several foreign jurisdictions		Non-exclusive rights for therapeutic purposes
Stanford University	RNAi uses <i>in vivo</i> in mammalian liver	7/23/2001	M.A. Kay, A.P. McCaffrey	AU 2002326410 (Australia) Additional applications pending in the U.S. and several foreign jurisdictions	7/23/2021	Exclusive rights for therapeutic purposes



- \* For applications filed after June 7, 1995, the patent term generally is 20 years from the earliest application filing date. However, under the Drug Price Competition and Patent Term Extension Act of 1984, known as the Hatch-Waxman Act, we may be able to apply for patent term extensions for our U.S. patents. We cannot predict whether or not any patent term extensions will be granted or the length of any patent term extension that might be granted.

**Table of Contents**

\*\* We hold co-exclusive therapeutic rights with Isis. However, Isis has agreed not to license such rights to any third party, except in the context of a collaboration in which Isis plays an active role.

\*\*\* We hold exclusive rights to the interest owned by three co-owners. A separate entity, UMass, has licensed its purported interest separately to third parties.

We believe that we have a strong portfolio of broad rights to fundamental RNAi patents and patent applications. Many of these rights are exclusive, which we believe prevents potential competitors from commercializing products in the field of RNAi without taking a license from us. In securing these rights, we have focused on obtaining the strongest rights for those intellectual property assets we believe will be most important in providing competitive advantage with respect to RNAi therapeutic products.

We believe that the Crooke patent series, issued in several countries around the world, covers the use of all modified oligonucleotides to achieve enzyme-mediated cleavage of a target mRNA and, as such, has broad issued claims that cover RNAi. We have obtained rights to the Crooke patents through a license agreement with Isis. Under the terms of our amended and restated Isis agreement, Isis agreed not to grant licenses under these patents to any other organization for oligonucleotide products designed to work through an RNAi mechanism, except in the context of a collaboration in which Isis plays an active role.

Through our acquisition of Ribopharma AG, now known as Alnylam Europe, we own the entire Kreutzer-Limmer patent portfolio, which includes pending applications in the United States and many countries worldwide. The first patent to issue in the Kreutzer-Limmer series (EP 1144623) was granted in Europe in 2002, and specifically covered the use of small dsRNAs as therapeutics. This patent was revoked in appeal. The second European Kreutzer-Limmer patent (EP 1214945) to issue in the series was granted in Europe in 2005. This patent covers dsRNA structures of 15 to 49 successive nucleotide pairs in length. In January 2009, the European Patent Office, or EPO, ruled in favor of the opposing parties in an opposition proceeding related to the second Kreutzer-Limmer patent. We have appealed this ruling. In December 2008, the EPO granted a third patent in the Kreutzer-Limmer series (EP 1550719). This patent covers therapeutic dsRNAs which are 15 to 21 consecutive nucleotide pairs in length. The third Kreutzer-Limmer patent has been opposed. In July 2009, the EPO issued a Notice of Intent to Grant for a fourth patent in the Kreutzer-Limmer series (EP App. No. 02702247.4). This patent covers methods and medicaments having dsRNAs that are less than 25 nucleotides in length having a 3' nucleotide overhang on the antisense strand which inhibit anti-apoptotic genes in tumor cells. We have also received grants for patents in the Kreutzer-Limmer series in several other countries, as reflected in the table above. The decision with respect to EP 1144623 and the outcome of the EP 1214945 opposition will only affect the granted or pending claims of other members of the Kreutzer-Limmer patent series to the extent the same issue arises in the formal examination or post-grant review proceedings of the other members of the series. We do not expect this to occur, but in the event it does, the ruling in the former proceeding would be controlling.

The Glover patent series has resulted in several patent grants, including in Europe (EP 1230375). The European Glover patent was revoked in June 2008 during opposition proceedings and our appeal of this decision is pending. Broad claims from this patent cover dsRNAs of any length or structure as mediators of RNAi in mammalian systems. We have an exclusive license to the Glover patent for therapeutic uses from Cancer Research Technology Limited.

The Tuschl patent applications filed by Whitehead, MIT, UMass and Max-Planck-Gesellschaft zur Forderung der Wissenschaften E.V. on the invention by Dr. Tuschl and his colleagues, which we call the Tuschl I patent series, cover compositions and methods important for RNAi discovery. While none of the applications in this family have been granted in the United States, the EPO recently granted patent EP 1309726. This patent consists of 19 claims broadly covering *in vitro* RNAi methods, including methods of reducing the expression of a gene, including those of

mammalian or viral origin, with dsRNAs between 21 and 23 nucleotides in length. In addition, the patent also includes claims covering methods of examining the function of a gene, as well as the use of both unmodified and chemically modified dsRNAs. The Tuschl I series has also been granted in New Zealand (Patent 522045) and recently allowed in Korea. We are the exclusive licensee of the ownership interests of the Max Planck Society, MIT and Whitehead in the Tuschl I patent series for RNAi therapeutics.

The Tuschl patent applications filed by Max Planck Gesellschaft zur Förderung der Wissenschaften e.V. on the invention by Dr. Tuschl and his colleagues, which we call the Tuschl II patent series, cover what we believe are key

## **Table of Contents**

structural features of siRNAs. Specifically, the Tuschl II patents and patent applications include claims directed to synthetic siRNAs and the use of chemical modifications to stabilize siRNAs. In June 2006, the United States Patent and Trademark Office, or USPTO, issued U.S. Patent No. 7,056,704 and in July 2006 the USPTO issued U.S. Patent No. 7,078,196, each covering methods of making dsRNAs having a 3' overhang structure. In September 2007, the EPO granted broad claims for the Tuschl II patent in Europe (EP 1407044). Five parties have filed Notices of Opposition in the EPO against EP 1407044. The Japanese Patent Office has granted the Tuschl II patent in Japan (JP 4 095 895) and the Chinese Patent Office has granted the Tuschl II patent in China (CN 1568373). We have also received grants for patents in the Tuschl II series in several other countries, as reflected in the table above. We have obtained an exclusive license to claims in the Tuschl II patent series uniquely covering the use of RNAi for therapeutic purposes.

The Fire and Mello patent owned by the Carnegie Institution covers the use of dsRNAs to induce RNAi. The Carnegie Institution has made this patent broadly available for licensing and we, like many companies, have taken a non-exclusive license to the patent for therapeutic purposes. We believe, however, that the claims of the Fire and Mello patent do not cover the structural features of dsRNAs that are important for the biological activity of siRNAs in mammalian cells. We believe that these specific features are the subjects of the Crooke, Kreutzer-Limmer, Glover and Tuschl II patents and patent applications for which we have secured exclusive rights.

The other pending patent applications listed in the table above either provide further coverage for structural features of siRNAs or relate to the use of siRNAs in mammalian cells. For some of these, we have exclusive rights, and for others, we have non-exclusive rights. In addition, in December 2008, we acquired the intellectual property assets of Nucleonics, Inc., a privately held biotechnology company. This acquisition included over 100 active patent filings, including 15 patents that have been granted worldwide, of which five have been granted in the United States and Europe. With this acquisition, we obtained patents and patent applications with early priority dates, notably the Li & Kirby, Pachuk I and Giordano patent families, that cover broad structural features of RNAi therapeutics, thus extending the breadth of our fundamental intellectual property.

### ***Intellectual Property Related to Chemical Modifications***

Our amended and restated collaboration and license agreement with Isis provides us with rights to practice the inventions covered by over 200 issued patents worldwide, as well as rights based on future chemistry patent applications through April 2014. These patents will expire both in and outside the United States generally between 2009 and 2029, subject to any potential patent term extensions and/or supplemental protection certificates extending such term extensions in countries where such extensions may become available. These inventions cover chemical modifications we may wish to incorporate into our RNAi therapeutic products. Under the terms of our amended and restated license agreement, Isis agreed not to grant licenses under these patents to any other organization for dsRNA products designed to work through an RNAi mechanism, except in the context of a collaboration in which Isis plays an active role.

In addition to licensing these intellectual property rights from Isis, we are also working to develop our own proprietary chemical modifications that may be incorporated into siRNAs to endow them with drug-like properties. We have filed a large number of patent applications relating to these novel and proprietary chemical modifications.

With the combination of the technology we have licensed from Isis, U.S. Patent No. 7,078,196, a patent in the Tuschl II patent series, and our own patent application filings, we possess issued claims that cover methods of making siRNAs that incorporate any of various chemical modifications, including the use of phosphorothioates, 2'-O-methyl, and/or 2'-fluoro modifications. These modifications are believed to be important for achieving drug-like properties for RNAi therapeutics. We hold exclusive worldwide rights to these claims for RNAi therapeutics.

### ***Intellectual Property Related to siRNAs Directed to Specific Targets***

We have filed a number of patent applications claiming specific siRNAs directed to various gene targets that correlate to specific diseases. While there may be a significant number of competing applications filed by other organizations claiming siRNAs to treat the same gene target, we were among the first companies to focus and file on RNAi therapeutics, and thus, we believe that a number of our patent applications may predate competing applications that others may have filed. Reflecting this, in August 2005, the EPO granted a broad patent,

## **Table of Contents**

which we call the Kreutzer-Limmer II patent, with 103 allowed claims on therapeutic compositions, methods and uses comprising siRNAs that are complementary to mRNA sequences in over 125 disease target genes. In July 2009, the EPO ruled in our favor in an opposition proceeding related to the Kreutzer-Limmer II patent. The decision has been appealed by the opponents. The Kreutzer-Limmer II patent will expire on January 9, 2022, subject to any potential patent term extensions and/or supplemental protection certificates extending such term extensions in countries where such extensions may become available. Some of these claimed gene targets are being pursued by our development and pre-clinical programs, such as those expressed by viral pathogens including RSV and influenza virus. In addition, the claimed targets include oncogenes, cytokines, cell adhesion receptors, angiogenesis targets, apoptosis and cell cycle targets, and additional viral disease targets, such as hepatitis C virus and HIV. The Kreutzer-Limmer II patent series is pending in the United States and many foreign countries. Moreover, a patent in the Tuschl II patent series, U.S. Patent No. 7,078,196, claims methods of preparing siRNAs that mediate cleavage of an mRNA in mammalian cells and, therefore, covers methods of making siRNAs directed toward any and all target genes. We hold exclusive worldwide rights to these claims for RNAi therapeutics.

With respect to specific siRNAs, we believe that patent coverage will result from demonstrating that particular compositions exert suitable biological and therapeutic effects. Accordingly, we are focused on achieving such demonstrations for siRNAs in key therapeutic programs.

### ***Intellectual Property Related to the Delivery of siRNAs to Cells***

We are pursuing internal research and collaborative approaches regarding the delivery of siRNAs to mammalian cells. These approaches include exploring technology that may allow delivery of siRNAs to cells through the use of cationic lipids, cholesterol and carbohydrate conjugation, peptide and antibody-based targeting, and polymer conjugations. Our collaborative efforts include working with academic and corporate third parties to examine specific embodiments of these various approaches to delivery of siRNAs to appropriate cell tissue, and in-licensing of the most promising technology. For example, we have obtained an exclusive license from UBC and Tekmira in the field of RNAi therapeutics to intellectual property covering cationic liposomes and their use to deliver nucleic acid to cells. The issued United States patents and foreign counterparts, including the Semple (U.S. Patent No 6,858,225) and Wheeler (U.S. Patent Nos. 5,976,567 and 6,815,432) patents, cover compositions, methods of making and methods of using cationic liposomes to deliver agents, such as nucleic acid molecules, to cells. These patents will expire both in and outside the United States on October 30, 2017, January 6, 2015 and June 7, 2015, respectively, subject to any potential patent term extensions and/or supplemental protection certificates extending such term extensions in countries where such extensions may become available.

### ***Intellectual Property Related to Our Development Candidates***

As our development pipeline matures, we have made and plan to continue to make patent filings that claim all aspects of our development candidates, including dose, method of administration and manufacture.

### ***Patent Pool***

In July 2009, we announced that we will contribute more than 1,500 patents or pending patent applications in our RNAi technology patent estate to a patent pool established by GSK in March 2009. We are the first company to add its patents to the approximately 800 patent filings GSK provided to the pool. The patent pool was formed to aid in the discovery and development of new medicines for the treatment of 16 neglected tropical diseases, or NTDs, as defined by the FDA, in the world's least developed countries. Through our contribution to the patent pool, we are providing RNAi intellectual property, technology and know-how on a royalty-free, non-profit basis worldwide to research, develop and manufacture therapies for use in the least developed countries through licensing agreements with qualified third parties. Such organizations will be engaged in research efforts focused on discovery of new medicines

for NTDs. In January 2010, we and GSK announced the appointment of BIO Ventures for Global Health, or BVGH, to administer the patent pool. As the patent pool's administrator, BVGH will organize disease-specific meetings that identify the gaps in expertise and intellectual property that currently exist in product development for NTDs. BVGH will then help global health researchers work with industry to fill these gaps so that the resources made available by companies will be used to create medicines for NTDs faster and more efficiently.

## **Table of Contents**

### ***Intellectual Property Challenges***

As the field of RNAi therapeutics is maturing, patent applications are being fully processed by national patent offices around the world. There is uncertainty about which patents will issue, and, if they do, as to when, to whom, and with what claims. It is likely that there will be significant litigation and other proceedings, such as interference, reexamination and opposition proceedings, in various patent offices relating to patent rights in the RNAi field. For example, as noted above, various third parties have initiated oppositions to patents in our Kreutzer-Limmer and Tuschl II series in the EPO, as well as in other jurisdictions. We expect that additional oppositions will be filed in the EPO and elsewhere, and other challenges will be raised relating to other patents and patent applications in our portfolio. In many cases, the possibility of appeal exists for either us or our opponents, and it may be years before final, unappealable rulings are made with respect to these patents in certain jurisdictions. Given the importance of our intellectual property portfolio to our business operations, we intend to vigorously enforce our rights and defend against challenges that have arisen or may arise in this area.

In June 2009, we joined with Max-Planck-Gesellschaft Zur Forderung Der Wissenschaften E.V. and Max-Planck-Innovation GmbH, collectively, Max Planck, in taking legal action against Whitehead, MIT and UMass. The complaint, initially filed in Suffolk County Superior Court in Boston, Massachusetts and subsequently removed to the U.S. District Court for the District of Massachusetts, alleges, among other things, that the defendants have improperly prosecuted the Tuschl I patent applications and wrongfully incorporated inventions covered by the Tuschl II patent applications into the Tuschl I patent applications, thereby potentially damaging the value of inventions reflected in the Tuschl I and Tuschl II patent applications. In the field of RNAi therapeutics, we are the exclusive licensee of the Tuschl I patent applications from Max Planck, MIT and Whitehead, and of the Tuschl II patent applications from Max Planck.

The complaint seeks to enjoin the defendants from taking any further action in connection with the prosecution of any Tuschl I application, a declaratory judgment and unspecified monetary damages. In August 2009, the court denied our motion for a preliminary injunction. In addition, in August 2009, Whitehead and UMass filed counterclaims against us and Max Planck, including for breach of contract. A trial on the merits was originally scheduled to begin in February 2010. In January 2010, we and Max Planck filed a motion for leave to file an amended complaint expanding upon the allegations in the original complaint. In January 2010, the court granted this motion allowing our amended complaint and postponed the start of the trial. We currently expect the trial to start in June 2010.

In addition, in September 2009, the USPTO granted Max Planck's petition to revoke power of attorney in connection with the prosecution of the Tuschl I patent application. This action prevents the defendants from filing any papers with the USPTO in connection with further prosecution of the Tuschl I patent application without the agreement of Max Planck. Whitehead's petition to overturn the ruling on Max Planck's petition was denied.

Although we, along with Max Planck, are vigorously asserting our rights in this case, litigation is subject to inherent uncertainty and a court could ultimately rule against us. In addition, litigation is costly and may divert the attention of our management and other resources that would otherwise be engaged in running our business.

### **Competition**

The pharmaceutical marketplace is extremely competitive, with hundreds of companies competing to discover, develop and market new drugs. We face a broad spectrum of current and potential competitors, ranging from very large, global pharmaceutical companies with significant resources, to other biotechnology companies with resources and expertise comparable to our own and to smaller biotechnology companies with fewer resources and expertise than we have. We believe that for most or all of our drug development programs, there will be one or more competing programs under development at other companies. In many cases, the companies with competing programs will have



access to greater resources and expertise than we do and may be more advanced in those programs.

## **Table of Contents**

The competition we face can be grouped into three broad categories:

other companies working to develop RNAi therapeutic products;

companies developing technology known as antisense, which, like RNAi, attempts to silence the activity of specific genes by targeting the mRNAs copied from them; and

marketed products and development programs for therapeutics that treat the same diseases for which we may also be developing treatments.

We are aware of several other companies that are working to develop RNAi therapeutic products. Some of these companies are seeking, as we are, to develop chemically synthesized siRNAs as drugs. Others are following a gene therapy approach, with the goal of treating patients not with synthetic siRNAs but with synthetic, exogenously-introduced genes designed to produce siRNA-like molecules within cells.

Companies working on chemically synthesized siRNAs include Merck & Co., Inc., or Merck, through its subsidiary Sirna Therapeutics, Inc., or Sirna, Roche, Takeda, Kyowa Hakko Kirin, Pfizer Inc.'s Research Technology Center, MDRNA, Inc., Calando, Quark, Silence Therapeutics plc, RXi Pharmaceuticals Corporation, Tekmira, Sylentis S.A., Dicerna Pharmaceuticals, Inc., Opko Health, Inc., ZaBeCor Pharmaceuticals and Abbott Laboratories. Many of these companies have licensed our intellectual property.

Companies working on gene therapy approaches to RNAi therapeutics include Benitec, Cequent Pharmaceuticals, Inc. and Targeted Genetics Corporation.

Companies working on microRNA-based therapeutics include Rosetta Genomics, Santaris Pharma A/S, miRagen Therapeutics, Inc. and Asuragen, Inc.

Antisense technology uses short, single-stranded, DNA-like molecules to block mRNAs encoding specific proteins. An antisense oligonucleotide, or ASO, contains a sequence of bases complementary to a sequence within its target mRNA, enabling it to attach to the mRNA by base-pairing. The attachment of the ASO may lead to breakdown of the mRNA, or may physically block the mRNA from associating with the protein synthesis machinery of the cell. In either case, production of the protein encoded by the mRNA may be reduced. Typically, the backbone of an ASO, the linkages that hold its constituent bases together, will carry a number of chemical modifications that do not exist in naturally occurring DNA. These modifications are intended to improve the stability and pharmaceutical properties of the ASO.

While we believe that RNAi drugs may potentially have significant advantages over ASOs, including greater potency and specificity, others are developing ASO drugs that are currently at a more advanced stage of development than RNAi drugs. For example, Isis has developed an ASO drug, Vitravene<sup>®</sup>, which is currently on the market, and has several ASO product candidates in clinical trials. In addition, a number of other companies have product candidates in various stages of pre-clinical and clinical development. Included in these companies are Genta Incorporated and AVI BioPharma, Inc. Because of their later stage of development, ASOs, rather than siRNAs, may become the preferred technology for drugs that target mRNAs in order to turn off the activity of specific genes.

The competitive landscape continues to expand and we expect that additional companies will initiate programs focused on the development of RNAi therapeutic products using the approaches described above as well as potentially new approaches that may result in the more rapid development of RNAi therapeutics or more effective technologies for RNAi drug development or delivery.

*Competing Drugs for RSV*

The only product currently approved for the treatment of RSV infection is Ribavirin, which is marketed as Virazole by Valeant. This is approved only for treatment of hospitalized infants and young children with severe lower respiratory tract infections due to RSV. While it is also used to treat RSV infection in lung transplant patients, no randomized controlled trials of Ribavirin have been conducted in the lung transplant patient population. Ribavirin has been reported to have limited efficacy and limited anti-viral activity against RSV. Moreover, administration of the drug is complicated and requires elaborate environmental reclamation devices because of

## **Table of Contents**

potential harmful effects on health care personnel exposed to the drug. According to published reports by Valeant, sales of Virazole were \$12.3 million in 2008.

Other current RSV therapies consist of primarily treating the symptoms or preventing the viral infection by using the prophylactic drug Synagis (palivizumab), which is marketed by MedImmune. Synagis is a neutralizing monoclonal antibody that prevents the virus from infecting the cell by blocking the RSV F protein. Synagis is injected intramuscularly once a month during the RSV season to prevent infection. According to published reports by MedImmune and AstraZeneca PLC, which acquired MedImmune during 2007, worldwide Synagis sales were approximately \$1.1 billion in 2009. MedImmune is also developing motavizumab (formerly known as Numax<sup>®</sup>), a humanized monoclonal antibody, which is being evaluated for its potential to prevent serious lower respiratory tract disease caused by RSV in pediatric patients at high risk of contracting RSV disease. MedImmune submitted a biologics license application for motavizumab to the FDA in early 2008 and received a complete response letter from the FDA in November 2008 requesting additional information. MedImmune submitted a response to the FDA in December 2009. MedImmune has also initiated a Phase I/IIa clinical trial of a live, attenuated intranasal vaccine in development to help prevent severe RSV infections and has several ongoing Phase I trials to evaluate a second live, attenuated intranasal vaccine in development to help prevent severe lower respiratory tract disease caused by RSV or parainfluenza virus 3. In addition, Novartis has a small molecule drug, RSV604, licensed from Arrow Therapeutics Ltd, which was last reported as being in Phase II clinical trials. RSV604 is an oral drug that targets the viral N protein.

### ***Competing Drugs for Liver Cancer***

There are a variety of surgical procedures, chemotherapeutics, radiation and other approaches that are used in the management of both primary and secondary liver cancer. However, for the majority of patients the prognosis remains poor with fatal outcomes within several months of diagnosis. In November 2007, the FDA approved Sorafenib, also called Nexavar<sup>®</sup>, for the treatment of un-resectable liver cancer. Nexavar is the product of Onyx Pharmaceuticals, Inc., developed in collaboration with Bayer Pharmaceuticals Corporation. Worldwide sales of Nexavar were \$843.5 million in 2009.

There are also a large number of drugs in various stages of clinical development as cancer therapeutics, although the efficacy and safety of these newer drugs are difficult to ascertain at this point of development.

### ***Competing Drugs for TTR-Mediated Amyloidosis (ATTR)***

Currently, liver transplantation is the only available treatment option for FAP. However, only a subset of FAP patients qualify for this costly and invasive procedure and, even following liver transplantation, the disease continues to progress for many patients, presumably due to normal TTR being deposited into preexisting fibrils. Moreover, there is a shortage of donors to provide healthy livers for transplantation into eligible patients. There are no existing disease-modifying treatments to address ATTR.

There are a few drugs in clinical development for the treatment of ATTR. FoldRx Pharmaceuticals, Inc. recently completed a Phase II/III trial of tafamidis for FAP and a Phase II trial of tafamidis for FAC. Tafamidis is a small-molecule compound that is intended to stabilize wild-type and variant TTR, prevent misfolding and inhibit the formation of TTR amyloid fibrils. In the Phase II/III study in patients suffering from FAP, tafamidis was found to halt disease progression, reduce the burden of disease after 18 months compared to placebo, and appeared to be safe and well tolerated. Researchers at Boston University, in collaboration with the National Institute of Neurological Disorders and Stroke, are currently conducting a Phase II/III study of diflunisal for the treatment of FAP. Diflunisal is a commercially available non-steroidal anti-inflammatory agent that has been found to stabilize TTR *in vitro*.

### ***Competing Drugs for Hypercholesterolemia***

The current standard of care for patients with hypercholesterolemia includes the use of several agents. Front line therapy consists of HMG CoA reductase inhibitors, commonly known as statins, which block production of cholesterol by the liver and increase clearance of LDL-c from the bloodstream. These include Lipitor, Zocor, Crestor and Pravachol. A different class of compounds, which includes Zetia and Vytorin, function by blocking cholesterol uptake from the diet and are utilized on their own or in combination with statins. Each of Lipitor, Crestor,

## **Table of Contents**

Zetia and Vytorin had sales of greater than \$1.0 billion during 2009, according to published reports. With regard to future therapies, mipomersen, formerly ISIS 301012, is a lipid-lowering drug targeting apolipoprotein B-100 being developed by Isis in collaboration with Genzyme Corporation that is currently in Phase III development. Top line data from a Phase III study evaluating mipomersen in patients with homozygous familial hypercholesterolemia demonstrated a 25% reduction in LDL-c after 26 weeks of treatment versus three percent for placebo ( $p < 0.001$ ). This study also met each of its three secondary endpoints of reduction in apoB, total cholesterol and non-HDL cholesterol (all  $p < 0.001$ ). A weekly injectable therapeutic, mipomersen is being developed primarily for patients at significant cardiovascular risk who are unable to achieve target cholesterol levels with statins alone or who are intolerant of statins.

### ***Competing Drugs for Huntington's Disease (HD)***

While certain drugs are currently used to treat some of the symptoms of HD, no drug has been approved in the United States for the treatment of the underlying disease. Current pharmacological therapy for HD is limited to the management or alleviation of neurobehavioral or movement abnormalities associated with the disease. No disease modifying, disease slowing or neuroprotective agent is currently approved or used to treat HD, although there are several drugs in development.

Avicena Group Inc.'s HD-02, an ultra-pure creatine, is a candidate for prophylactic use for HD which has shown potential neuroprotective properties in HD patients in Phase II trials. Medivation Inc.'s Dimebon<sup>®</sup> is an orally-available small molecule that is believed to block the mitochondrial permeability transition pore, or MPTP, the glutamate N-methyl D-aspartate, or NMDA, receptor and cholinesterase activity. The safety and efficacy of Dimebon is currently being investigated in an international Phase III trial, in collaboration with Pfizer Inc. Results from a Phase II trial completed in early 2008 showed significantly improved cognitive function in patients with mild-to-moderate HD over placebo.

### ***Other Competition***

Finally, for many of the diseases that are the subject of our RNAi therapeutics discovery programs, there are already drugs on the market or in development. However, notwithstanding the availability of these drugs or drug candidates, we believe there currently exists sufficient unmet medical need to warrant the advancement of RNAi therapeutic programs.

### **Regulatory Matters**

The research, testing, manufacture and marketing of drug products and their delivery systems are extensively regulated in the United States and the rest of the world. In the United States, drugs are subject to rigorous regulation by the FDA. The Federal Food, Drug, and Cosmetic Act and other federal and state statutes and regulations govern, among other things, the research, development, testing, manufacture, storage, record keeping, packaging, labeling, promotion and advertising, marketing and distribution of pharmaceutical products. Failure to comply with the applicable regulatory requirements may subject a company to a variety of administrative or judicially-imposed sanctions and the inability to obtain or maintain required approvals to test or market drug products. These sanctions could include warning letters, product recalls, product seizures, total or partial suspension of production or distribution, clinical holds, injunctions, fines, civil penalties or criminal prosecution.

The steps ordinarily required before a new pharmaceutical product may be marketed in the United States include non-clinical laboratory tests, animal tests and formulation studies, the submission to the FDA of an IND, which must become effective prior to commencement of clinical testing, adequate and well-controlled clinical trials to establish that the drug product is safe and effective for the indication for which FDA approval is sought, submission to the FDA

of a new drug application, or NDA, satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with current good manufacturing practice, or cGMP, requirements and FDA review and approval of the NDA. Satisfaction of FDA pre-market approval requirements typically takes several years, but may vary substantially depending upon the complexity of the product and the nature of the disease. Government regulation may delay or prevent marketing of potential products for a considerable period of time and impose costly procedures on a company's activities.

## **Table of Contents**

Success in early stage clinical trials does not necessarily assure success in later stage clinical trials. Data obtained from clinical activities, including the data derived from our clinical trials for ALN-RSV01 and ALV-VSP, is not always conclusive and may be subject to alternative interpretations that could delay, limit or even prevent regulatory approval. Even if a product receives regulatory approval, later discovery of previously unknown problems with a product, including new safety risks, may result in restrictions on the product or even complete withdrawal of the product from the market.

Non-clinical tests include laboratory evaluation of product chemistry and formulation, as well as animal testing to assess the potential safety and efficacy of the product. The conduct of the non-clinical tests and formulation of compounds for testing must comply with federal regulations and requirements. The results of non-clinical testing are submitted to the FDA as part of an IND, together with manufacturing information, analytical and stability data, a proposed clinical trial protocol and other information.

A 30-day waiting period after the filing of an IND is required prior to such application becoming effective and the commencement of clinical testing in humans. If the FDA has not commented on, or questioned, the application during this 30-day waiting period, clinical trials may begin. If the FDA has comments or questions, these must be resolved to the satisfaction of the FDA prior to commencement of clinical trials. The IND approval process can result in substantial delay and expense. We, an institutional review board, or IRB, or the FDA may, at any time, suspend, terminate or impose a clinical hold on ongoing clinical trials. If the FDA imposes a clinical hold, clinical trials cannot commence or recommence without FDA authorization and then only under terms authorized by the FDA.

Clinical trials involve the administration of an investigational new drug to healthy volunteers or patients under the supervision of a qualified investigator. Clinical trials must be conducted in compliance with federal regulations and requirements, including good clinical practices, or GCPs, under protocols detailing, among other things, the objectives of the trial and the safety and effectiveness criteria to be evaluated. Each protocol involving testing on human subjects in the United States, or in foreign countries if such tests are intended to support approval in the United States, must be submitted to the FDA as part of the IND. The study protocol and informed consent information for patients in clinical trials must be submitted to IRBs for approval prior to initiation of the trial.

Clinical trials to support NDAs for marketing approval are typically conducted in three sequential phases, which may overlap or be combined. In Phase I, the initial introduction of the drug into healthy human subjects or patients, the drug is tested to primarily assess safety, tolerability, pharmacokinetics, pharmacological actions and metabolism associated with increasing doses. Phase II usually involves trials in a limited patient population, to assess the optimum dosage, identify possible adverse effects and safety risks, and provide preliminary support for the efficacy of the drug in the indication being studied.

If a compound demonstrates evidence of effectiveness and an acceptable safety profile in Phase II trials, Phase III trials are undertaken to further evaluate clinical efficacy and to further test for safety in an expanded patient population, typically at geographically dispersed clinical trial sites. Phase I, Phase II or Phase III testing of any product candidates may not be completed successfully within any specified time period, if at all. After successful completion of the required clinical testing, generally an NDA is prepared and submitted to the FDA.

We believe that any RNAi product candidate we develop, whether for RSV, liver cancers, ATTR, hypercholesterolemia, HD or the various indications targeted in our pre-clinical discovery programs, will be regulated as a new drug by the FDA. FDA approval of an NDA is required before marketing of the product may begin in the United States. The NDA must include the results of extensive clinical and other testing, as described above, and a compilation of data relating to the product's pharmacology, chemistry, manufacture and controls. In addition, an NDA for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration must contain data assessing the safety and efficacy for the claimed indication in all relevant pediatric subpopulations,



and support dosing and administration for each pediatric subpopulation for which the drug is shown to be safe and effective. In some circumstances, the FDA may grant deferrals for the submission of some or all pediatric data, or full or partial waivers. The cost of preparing and submitting an NDA is substantial. Under federal law, NDAs are subject to substantial application user fees and the sponsor of an approved NDA is also subject to annual product and establishment user fees.

## **Table of Contents**

The FDA has 60 days from its receipt of an NDA to determine whether the application will be accepted for filing based on the agency's threshold determination that the NDA is sufficiently complete to permit substantive review. Once the submission is accepted for filing, the FDA begins an in-depth review of the NDA. The review process is often significantly extended by FDA requests for additional information or clarification regarding information already provided in the submission. The FDA may also refer applications for novel drug products or drug products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee. The FDA normally also will conduct a pre-approval inspection to ensure the manufacturing facility, methods and controls are adequate to preserve the drug's identity, strength, quality, purity and stability, and are in compliance with regulations governing cGMPs.

If the FDA evaluation of the NDA and the inspection of manufacturing facilities are favorable, the FDA may issue an approval letter, which authorizes commercial marketing of the drug with specific prescribing information for a specific indication. As a condition of NDA approval, the FDA may require post-approval testing, including Phase IV trials, and surveillance to monitor the drug's safety or efficacy and may impose other conditions, including labeling restrictions, which can materially impact the potential market and profitability of the drug. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

While we believe that any RNAi therapeutic we develop will be regulated as a new drug under the Federal Food, Drug, and Cosmetic Act, the FDA could decide to regulate certain RNAi therapeutic products as biologics under the Public Health Service Act. Biologics must have a biologics license application, or BLA, approved prior to commercialization. Like NDAs, BLAs are subject to user fees. To obtain BLA approval, an applicant must provide non-clinical and clinical evidence and other information to demonstrate that the biologic product is safe, pure and potent, and like NDAs, must complete clinical trials that are typically conducted in three sequential phases (Phase I, II and III). Additionally, the applicant must demonstrate that the facilities in which the product is manufactured, processed, packaged or held meet standards, including cGMPs and any additional standards in the license designed to ensure its continued safety, purity and potency. Biologics establishments are subject to pre-approval inspections. The review process for BLAs is also time consuming and uncertain, and BLA approval may be conditioned on post-approval testing and surveillance. Once granted, BLA approvals may be suspended or revoked under certain circumstances, such as if the product fails to conform to the standards established in the license.

Once an NDA or BLA is approved, a product will be subject to certain post-approval requirements, including requirements for adverse event reporting, submission of periodic reports, recordkeeping, product sampling and distribution. Additionally, the FDA also strictly regulates the promotional claims that may be made about prescription drug products and biologics. In particular, a drug or biologic may not be promoted for uses that are not approved by the FDA as reflected in the product's approved labeling. In addition, the FDA requires substantiation of any claims of superiority of one product over another, including that such claims be proven by adequate and well-controlled head-to-head clinical trials. To the extent that market acceptance of our products may depend on their superiority over existing therapies, any restriction on our ability to advertise or otherwise promote claims of superiority, or requirements to conduct additional expensive clinical trials to provide proof of such claims, could negatively affect the sales of our products or our costs. We must also notify the FDA of any change in an approved product beyond variations already allowed in the approval. Certain changes to the product, its labeling or its manufacturing require prior FDA approval and may require the conduct of further clinical investigations to support the change. Such approvals may be expensive and time-consuming and, if not approved, the FDA will not allow the product to be marketed as modified.

If the FDA's evaluation of the NDA or BLA submission or manufacturing facilities is not favorable, the FDA may refuse to approve the NDA or BLA or issue a complete response letter. The complete response letter describes the

deficiencies that the FDA has identified in an application and, when possible, recommends actions that the applicant might take to place the application in condition for approval. Such actions may include, among other things, conducting additional safety or efficacy studies after which the sponsor may resubmit the application for further review. Even with the completion of this additional testing or the submission of additional requested

**Table of Contents**

information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. With limited exceptions, the FDA may withhold approval of an NDA or BLA regardless of prior advice it may have provided or commitments it may have made to the sponsor.

Some of our product candidates may need to be administered using specialized drug delivery systems. We may rely on drug delivery systems that are already approved to deliver drugs like ours to similar physiological sites or, in some instances, we may need to modify the design or labeling of the legally available device for delivery of our product candidate. In such an event, the FDA may regulate the product as a combination product or require additional approvals or clearances for the modified device. In addition, to the extent the delivery device is owned by another company, we would need that company's cooperation to implement the necessary changes to the device and to obtain any additional approvals or clearances. Obtaining such additional approvals or clearances, and cooperation of other companies, when necessary, could significantly delay, and increase the cost of obtaining marketing approval, which could reduce the commercial viability of a product candidate. To the extent that we rely on previously unapproved drug delivery systems, we may be subject to additional testing and approval requirements from the FDA above and beyond those described above.

Once an NDA or BLA is approved, the product covered thereby becomes a listed drug that can, in turn, be cited by potential competitors in support of approval of an abbreviated new drug application, or ANDA, upon expiration of relevant patents, if any. An approved ANDA provides for marketing of a drug product that has the same active ingredients in the same strength, dosage form and route of administration as the listed drug and has been shown through bioequivalence testing to be therapeutically equivalent to the listed drug. There is no requirement, other than the requirement for bioequivalence testing, for an ANDA applicant to conduct or submit results of non-clinical or clinical tests to prove the safety or effectiveness of its drug product. Drugs approved in this way are commonly referred to as generic equivalents to the listed drug, are listed as such by the FDA and can often be substituted by pharmacists under prescriptions written for the original listed drug.

Federal law provides for a period of three years of exclusivity following approval of a listed drug that contains previously approved active ingredients but is approved in a new dosage, dosage form, route of administration or combination, or for a new use, if the FDA deems that the sponsor was required to provide support from new clinical trials to obtain such marketing approval. During such three-year exclusivity period, the FDA cannot grant approval of an ANDA to commercially distribute a generic version of the drug based on that listed drug. However, the FDA can approve generic or other versions of that listed drug, such as a drug that is the same in every way but its indication for use, and thus the value of such exclusivity may be undermined. Federal law also provides a period of up to five years exclusively following approval of a drug containing no previously approved active ingredients, during which ANDAs for generic versions of those drugs cannot be submitted unless the submission accompanies a challenge to a listed patent, in which case the submission may be made four years following the original product approval.

Additionally, in the event that the sponsor of the listed drug has properly informed the FDA of patents covering its listed drug, applicants submitting an ANDA referencing that drug are required to make one of four patent certifications, including certifying that it believes one or more listed patents are invalid or not infringed. If an applicant certifies invalidity or non-infringement, it is required to provide notice of its filing to the NDA sponsor and the patent holder. If the patent holder then initiates a suit for patent infringement against the ANDA sponsor within 45 days of receipt of the notice, the FDA cannot grant effective approval of the ANDA until either 30 months have passed or there has been a court decision holding that the patents in question are invalid, unenforceable or not infringed. If the patent holder does not initiate a suit for patent infringement within the 45 days, the ANDA may be approved immediately upon successful completion of FDA review, unless blocked by a regulatory exclusivity period. If the ANDA applicant certifies that it does not intend to market its generic product before some or all listed patents on the listed drug expire, then the FDA cannot grant effective approval of the ANDA until those patents expire. The first of the ANDA applicants submitting substantially complete applications certifying that one or more listed patents

for a particular product are invalid or not infringed may qualify for an exclusivity period of 180 days running from when the generic product is first marketed, during which subsequently submitted ANDAs cannot be granted effective approval. The 180-day generic exclusivity can be forfeited in various ways, including if the first applicant does not market its product within specified statutory timelines. If more than one applicant files a substantially complete ANDA on the same day, each such first applicant will be entitled to share the 180-day

## **Table of Contents**

exclusivity period, but there will only be one such period, beginning on the date of first marketing by any of the first applicants.

From time to time, legislation is drafted and introduced in Congress that could significantly change the statutory provisions governing the approval, manufacturing and marketing of drug products. In addition, FDA regulations and guidance are often revised or reinterpreted by the agency in ways that may significantly affect our business and development of our product candidates and any products that we may commercialize. It is impossible to predict whether additional legislative changes will be enacted, or FDA regulations, guidance or interpretations changed, or what the impact of any such changes may be.

## **Foreign Regulation of New Drug Compounds**

In addition to regulations in the United States, we are subject to a variety of regulations in other jurisdictions governing, among other things, clinical trials and any commercial sales and distribution of our products.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in all or most foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application much like the IND prior to the commencement of human clinical trials. In Europe, for example, a clinical trial application, or CTA, must be submitted to each country's national health authority and an independent ethics committee, much like the FDA and IRB, respectively. Once the CTA is approved in accordance with a country's requirements, clinical trial development may proceed. Similarly, all clinical trials in Australia require review and approval of clinical trial proposals by an ethics committee, which provides a combined ethical and scientific review process.

The requirements and process governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, the clinical trials must be conducted in accordance with GCP, which have their origin in the World Medical Association's Declaration of Helsinki, the applicable regulatory requirements, and guidelines developed by the International Conference on Harmonization, or ICH, for GCP practices in clinical trials.

The approval procedure also varies among countries and can involve requirements for additional testing. The time required may differ from that required for FDA approval and may be longer than that required to obtain FDA approval. Although there are some procedures for unified filings in the EU, in general, each country has its own procedures and requirements, many of which are time consuming and expensive. Thus, there can be substantial delays in obtaining required approvals from foreign regulatory authorities after the relevant applications are filed.

In Europe, marketing authorizations may be submitted under a centralized or decentralized procedure. The centralized procedure is mandatory for the approval of biotechnology and many pharmaceutical products and provides for the grant of a single marketing authorization that is valid in all EU member states. The decentralized procedure is a mutual recognition procedure that is available at the request of the applicant for medicinal products that are not subject to the centralized procedure. We strive to choose the appropriate route of European regulatory filing to accomplish the most rapid regulatory approvals. However, our chosen regulatory strategy may not secure regulatory approvals on a timely basis or at all.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

## **Pharmaceutical Coverage, Pricing and Reimbursement**

Significant uncertainty exists as to the coverage and reimbursement status of any drug products for which we obtain regulatory approval. In the United States and markets in other countries, sales of any products for which we may receive regulatory approval for commercial sale will depend in part on the availability of reimbursement from third party payors. Third party payors include government health administrative authorities, managed care providers, private health insurers and other organizations. The process for determining whether a payor will provide coverage for a drug product may be separate from the process for setting the price or reimbursement rate

## **Table of Contents**

that the payor will pay for the drug product. Third party payors may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the FDA-approved drugs for a particular indication. These third party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. In addition, significant uncertainty exists as to the reimbursement status of newly approved healthcare product candidates. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain FDA approvals. Our product candidates may not be considered medically necessary or cost-effective. A payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Adequate third party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

Federal, state and local governments in the United States continue to consider legislation to limit the growth of healthcare costs, including the cost of prescription drugs. Future legislation could limit payments for pharmaceuticals such as the drug candidates that we are developing.

Different pricing and reimbursement schemes exist in other countries. In the European Community, governments influence the price of pharmaceutical products through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate systems under which products may be marketed only after a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular product candidate to currently available therapies. Other member states allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription drugs, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert a commercial pressure on pricing within a country.

The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and third party payors fail to provide adequate coverage and reimbursement. In addition, an increasing emphasis on managed care in the United States has increased and we expect will continue to increase the pressure on pharmaceutical pricing. Coverage policies and third party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

## **Hazardous Materials**

Our research and development processes involve the controlled use of hazardous materials, chemicals and radioactive materials and produce waste products. We are subject to federal, state and local laws and regulations governing the use, manufacture, storage, handling and disposal of hazardous materials and waste products. We do not expect the cost of complying with these laws and regulations to be material.

## **Manufacturing**

We have no commercial manufacturing capabilities. We may manufacture drug substance for use in IND-enabling toxicology studies in animals at our own facility, but we have not manufactured any such material to date and we do not anticipate manufacturing the substantial portion of such material or any drug substance or finished product for human clinical use ourselves. We have contracted with several third-party contract manufacturing organizations for the supply of drug substance and finished product to meet our testing needs for pre-clinical toxicology and clinical testing. Commercial quantities of any drugs that we may seek to develop will have to be manufactured in facilities, and by processes, that comply with FDA regulations and other federal, state and local regulations, as well as



comparable foreign regulations. We plan to rely on third parties to manufacture commercial quantities of drug substance and finished product for any product candidate that we successfully develop.

Under our agreements with Tekmira, we are obligated to utilize Tekmira for the manufacture of all LNP-formulated product candidates covered by Tekmira's intellectual property beginning during pre-clinical development and continuing through Phase II clinical trials. During 2009, we and Tekmira entered into a

**Table of Contents**

manufacturing and supply agreement under which we are committed to pay Tekmira a minimum of CAD\$11.2 million (representing U.S.\$9.2 million at the time of execution) through December 2011 for manufacturing services.

We believe we have sufficient manufacturing capacity through our third-party contract manufacturers to meet our current research and clinical needs. We believe that we have established, or will be able to develop or acquire, sufficient supply capacity to meet our anticipated needs. We also believe that with reasonably anticipated benefits from increases in scale and improvements in chemistry, we will be able to manufacture our product candidates at commercially competitive prices.

**Scientific Advisors**

We seek advice from our scientific advisory board, which consists of a number of leading scientists and physicians, on scientific and medical matters. Our scientific advisory board meets regularly to assess:

- our research and development programs;
- the design and implementation of our clinical programs;
- our patent and publication strategies;
- new technologies relevant to our research and development programs; and
- specific scientific and technical issues relevant to our business.

The current members of our scientific advisory board are:

<b>Name</b>	<b>Position/Institutional Affiliation</b>
David P. Bartel, Ph.D.	Member/Whitehead Institute for Biomedical Research; Professor/Massachusetts Institute of Technology; Investigator/Howard Hughes Medical Institute
Fritz Eckstein, Ph.D.	Professor/Max Planck Institute for Experimental Medicine
Robert S. Langer, Ph.D.	Institute Professor/Massachusetts Institute of Technology
Judy Lieberman, M.D., Ph.D.	Senior Investigator/Immune Disease Institute Harvard Medical School; Professor/Harvard Medical School; Director, Division of AIDS/Harvard Medical School
Stephen N. Oesterle, M.D.*	Senior Vice President for Medicine and Technology/Medtronic, Inc.
Paul R. Schimmel, Ph.D.	Ernest and Jean Hahn Professor/Skaggs Institute for Chemical Biology, The Scripps Research Institute
Phillip A. Sharp, Ph.D.	Institute Professor/The Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology
Markus Stoffel, M.D., Ph.D.	Professor/Institute of Molecular Systems Biology, Swiss Federal Institute of Technology (ETH) Zurich
Thomas H. Tuschl, Ph.D.	Professor/Rockefeller University; Investigator/Howard Hughes Medical Institute
Phillip D. Zamore, Ph.D.	Gretchen Stone Cook Professor/University of Massachusetts Medical School; Investigator/Howard Hughes Medical Institute

\* Dr. Oesterle participates as an observer on our scientific advisory board.

### **Employees**

As of January 31, 2010, we had 178 employees, 147 of whom were engaged in research and development. None of our employees are represented by a labor union or covered by a collective bargaining agreement, nor have we experienced work stoppages. We believe that relations with our employees are good.

**Table of Contents****Financial Information About Geographic Areas**

See the section entitled "Segment Information" appearing in Note 2 to our consolidated financial statements for financial information about geographic areas. The Notes to our consolidated financial statements are contained in Part II, Item 8 of this annual report on Form 10-K.

**Corporate Information**

The company comprises four entities, Alnylam Pharmaceuticals, Inc. and three wholly owned subsidiaries (Alnylam U.S., Inc., Alnylam Europe AG and Alnylam Securities Corporation). Alnylam Pharmaceuticals, Inc. is a Delaware corporation that was formed in May 2003. Alnylam U.S., Inc. is also a Delaware corporation that was formed in June 2002. Alnylam Securities Corporation is a Massachusetts corporation that was formed in December 2006. Alnylam Europe AG, which was incorporated in Germany in June 2000 under the name Ribopharma AG, was acquired by Alnylam Pharmaceuticals, Inc. in July 2003. Our principal executive office is located at 300 Third Street, Cambridge, Massachusetts 02142, and our telephone number is (617) 551-8200.

**Investor Information**

We maintain an internet website at <http://www.alnylam.com>. The information on our website is not incorporated by reference into this annual report on Form 10-K and should not be considered to be a part of this annual report on Form 10-K. Our website address is included in this annual report on Form 10-K as an inactive technical reference only. Our reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, including our annual reports on Form 10-K, our quarterly reports on Form 10-Q and our current reports on Form 8-K, and amendments to those reports, are accessible through our website, free of charge, as soon as reasonably practicable after these reports are filed electronically with, or otherwise furnished to, the Securities and Exchange Commission, or SEC. We also make available on our website the charters of our audit committee, compensation committee and nominating and corporate governance committee, our corporate governance guidelines and our code of business conduct and ethics. In addition, we intend to disclose on our web site any amendments to, or waivers from, our code of business conduct and ethics that are required to be disclosed pursuant to the SEC rules.

You may read and copy any materials we file with the SEC at the SEC's Public Reference Room at 100 F Street, NE, Washington, DC 20549. You may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC also maintains an Internet website that contains reports, proxy and information statements, and other information regarding Alnylam and other issuers that file electronically with the SEC. The SEC's Internet website address is <http://www.sec.gov>.

**Executive Officers of the Registrant**

<b>Name</b>	<b>Age</b>	<b>Position</b>
John M. Maraganore, Ph.D.	47	Chief Executive Officer and Director
Barry E. Greene	46	President and Chief Operating Officer
Akshay K. Vaishnav, M.D., Ph.D.	47	Senior Vice President, Clinical Research
Patricia L. Allen	48	Vice President of Finance and Treasurer

**John M. Maraganore, Ph.D.** has served as our Chief Executive Officer and as a member of our board of directors since December 2002. Dr. Maraganore also served as our President from December 2002 to December 2007. From April 2000 to December 2002, Dr. Maraganore served as Senior Vice President, Strategic Product Development at

Millennium Pharmaceuticals, Inc., a biopharmaceutical company. Dr. Maraganore serves as a member of the board of directors of the Biotechnology Industry Organization.

**Barry E. Greene** has served as our President and Chief Operating Officer since December 2007, as our Chief Operating Officer since he joined us in October 2003, and from February 2004 through December 2005, as our Treasurer. From February 2001 to September 2003, Mr. Greene served as General Manager of Oncology at Millennium Pharmaceuticals, Inc., a biopharmaceutical company. Mr. Greene serves as a member of the board of directors of Acorda Therapeutics, Inc., a biotechnology company.

**Table of Contents**

**Akshay K. Vaishnav, M.D., Ph.D.** has served as our Senior Vice President, Clinical Research since December 2008, and prior to that served as our Vice President, Clinical Research from the time he joined us in January 2006. From December 1998 through December 2005, Dr. Vaishnav held various positions at Biogen Idec Inc. (formerly Biogen, Inc.), a biopharmaceutical company, most recently as Senior Director, Translational Medicine. Dr. Vaishnav is a Member of the Royal College of Physicians, United Kingdom.

**Patricia L. Allen** has served as our Vice President of Finance since she joined us in May 2004, and as our Treasurer since January 2006. From March 1992 to May 2004, Ms. Allen held various positions at Alkermes, Inc., a biopharmaceutical company, most recently as Director of Finance. Ms. Allen is a certified public accountant.

**Table of Contents**

**ITEM 1A. RISK FACTORS**

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

**Risks Related to Our Business**

**Risks Related to Being 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 relevant cell tissue;

build and maintain a strong intellectual property portfolio;

gain regulatory acceptance for the development of our product candidates and market success for any products we commercialize;

develop and maintain successful strategic alliances; and

manage our spending as costs and expenses increase due to clinical trials, regulatory approvals and commercialization.

If we are unsuccessful in accomplishing these objectives, we may not be able to develop product candidates, commercialize products, raise capital, expand our business or continue our operations.

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

We have concentrated our efforts and therapeutic product research on RNAi technology, and our future success depends on the successful development of this technology and products based on it. Neither we nor any other company has received regulatory approval to market therapeutics utilizing siRNAs, the class of molecule we are trying to develop into drugs. The scientific discoveries that form the basis for our efforts to discover and develop new drugs are relatively new. The scientific evidence to support the feasibility of developing drugs based on these discoveries is both preliminary and limited. Skepticism as to the feasibility of developing RNAi therapeutics has been expressed in scientific literature. For example, there are potential challenges to achieving safe RNAi therapeutics based on the so-called off-target effects and activation of the interferon response.



## **Table of Contents**

Relatively few product candidates based on these discoveries have ever been tested in animals or humans. siRNAs may not naturally possess the inherent properties typically required of drugs, such as the ability to be stable in the body long enough to reach the tissues in which their effects are required, nor the ability to enter cells within these tissues in order to exert their effects. We currently have only limited data, and no conclusive evidence, to suggest that we can introduce these drug-like properties into siRNAs. We may spend large amounts of money trying to introduce these properties, and may never succeed in doing so. In addition, these compounds may not demonstrate in patients the chemical and pharmacological properties ascribed to them in laboratory studies, and they may interact with human biological systems in unforeseen, ineffective or harmful ways. As a result, we may never succeed in developing a marketable product, we may not become profitable and the value of our common stock will decline.

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

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

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

We have experienced significant operating losses since our inception. As of December 31, 2009, we had an accumulated deficit of \$299.8 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 and biotechnology companies or funding from contracts with the government or foundations, 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.

We believe that to become and remain consistently profitable, we must succeed in discovering, developing and commercializing novel drugs with significant market potential. This will require us to be successful in a range of challenging activities, including pre-clinical testing and clinical trial stages of development, obtaining regulatory approval for these novel drugs and manufacturing, marketing and selling them. We may never succeed in these activities, and may never generate revenues that are significant enough to achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. If we cannot become and remain consistently profitable, the market price of our common stock could decline. In addition, we may be unable to raise capital, expand our business, 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 product candidates;

**Table of Contents**

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, and obtain and maintain licenses to third-party intellectual property;

the resources, time and cost required for the preparation, filing, prosecution, maintenance and enforcement of patent claims;

the costs associated with legal activities arising in the course of our business activities;

progress in the research and development programs of Regulus; and

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

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

Even if our estimates are correct, we will be required to seek additional funding in the future and intend to do so through either collaborative arrangements, public or private equity offerings or debt financings, or a combination of one or more of these funding sources. Additional funds may not be available to us on acceptable terms or at all. In addition, the terms of any financing may adversely affect the holdings or the rights of our stockholders. For example, if we raise additional funds by issuing equity securities, 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. In May 2009, Novartis purchased 65,922 shares of our common stock at a purchase price of \$17.50 per share. These purchases allowed Novartis to maintain its ownership position of 13.4% of our outstanding common stock. While the exercise of these rights by Novartis has provided us with an aggregate of \$6.6 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 and, in the event of insolvency, would be paid before holders of equity securities received any distribution of corporate assets. If we are unable to obtain funding on a timely basis, we may be required to significantly 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.***

Our consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America. 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.

## **Table of Contents**

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

At December 31, 2009, we had \$435.3 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 and municipal obligations, 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, including the impact of 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. For example, due to market conditions, interest rates have fallen, and accordingly, our interest income decreased to \$5.4 million for the year ended December 31, 2009, from \$14.4 million for the year ended December 31, 2008. These market risks associated with our investment portfolio may have an adverse effect on our results of operations, liquidity and financial condition.

## **Risks Related to Our Dependence on Third Parties**

***Our 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 up to 30 exclusive targets to include in the collaboration, which number may be increased to 40 under certain circumstances and upon additional payments. Novartis pays the costs to develop these product candidates and will commercialize and market any products derived from this collaboration. For RNAi therapeutic products developed under the agreement, if any, we are entitled to receive milestone payments upon achievement of certain specified development and annual net sales events, up to an aggregate of \$75.0 million per therapeutic product, as well as royalties on the annual net sales, if any. If Novartis fails to successfully develop products using our technology, we may not receive any additional milestone payments or any royalty payments under this agreement. The Novartis agreement had an initial term of three years, with an option for two additional one-year extensions at the election of Novartis. In July 2009, Novartis elected to further extend the term of our collaboration agreement for the fifth and final planned year, through October 2010. Novartis may elect to terminate this collaboration prior to expiration in the event of a material uncured breach by us. Over the term of this agreement, we have received a substantial amount of funding from Novartis. If this collaboration is unsuccessful, if Novartis terminates this agreement prior to expiration or if Novartis does not elect to exercise its integration option described below, our business could be adversely affected.

Our agreement with Novartis also provides Novartis with a non-exclusive option to integrate into its operations our intellectual property relating to RNAi technology, excluding any technology related to delivery of nucleic acid based molecules. Novartis may exercise this integration option at any point during the research term, which term is currently expected to expire in the fourth quarter of 2010. In connection with the exercise of the integration option, Novartis would be required to make additional payments to us totaling \$100.0 million, payable in full at the time of exercise, which payments would include an option exercise fee, a milestone based on the overall success of the collaboration and pre-paid milestones and royalties that could become due as a result of future development of products using our technology. This amount would be offset by any license fees due to our licensors in accordance with the applicable license agreements with those parties. In addition, under this license grant, Novartis may be required to make milestone and royalty payments to us in connection with the development and commercialization of RNAi therapeutic products, if any. The license grant under the integration option, if exercised, would be structured similarly to our

non-exclusive platform licenses with Roche and Takeda. 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 that we choose to target. 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

**Table of Contents**

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 agreements with Roche and Takeda are important to our business. If Roche and/or Takeda do not successfully develop drugs pursuant to these agreements or these agreements result in competition between us and Roche and/or Takeda for the development of drugs targeting the same diseases, our business could be adversely affected.***

In July 2007, we entered into a license and collaboration agreement with Roche. Under the license and collaboration agreement we granted Roche a non-exclusive license to our intellectual property to develop and commercialize therapeutic products that function through RNAi, subject to our existing contractual obligations to third parties. The license is limited to the therapeutic areas of oncology, respiratory diseases, metabolic diseases and certain liver diseases and may be expanded to include up to 18 additional therapeutic areas, comprising substantially all other fields of human disease, as identified and agreed upon by the parties, upon payment to us by Roche of an additional \$50.0 million for each additional therapeutic area, if any. In addition, in exchange for our contributions under the collaboration agreement, for each RNAi therapeutic product developed by Roche, its affiliates, or sublicensees under the collaboration agreement, we are entitled to receive milestone payments upon achievement of specified development and sales events, totaling up to an aggregate of \$100.0 million per therapeutic target, together with royalty payments based on worldwide annual net sales, if any. In May 2008, we entered into a similar license and collaboration agreement with Takeda, which is limited to the therapeutic areas of oncology and metabolic diseases, and which may be expanded to include up to 20 additional therapeutic areas, comprising substantially all other fields of human disease, as identified and agreed upon by the parties, upon payment to us by Takeda of an additional \$50.0 million for each additional therapeutic area, if any. For each RNAi therapeutic product developed by Takeda, its affiliates and sublicensees, we are entitled to receive specified development and commercialization milestones, totaling up to \$171.0 million per product, together with royalty payments based on worldwide annual net sales, if any. 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 Roche or Takeda fails to successfully develop products using our technology, we may not receive any milestone or royalty payments under these agreements. In addition, even if Takeda is not successful in its efforts, for a period of five years we will be limited in our ability to form alliances with other parties in the Asia territory. We also have the option under the Takeda agreement, 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.

Finally, either Roche or Takeda could become a competitor of ours in the development of RNAi-based drugs targeting the same diseases that we choose to target. Each of these companies 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 either Roche or Takeda in the development of RNAi-based drugs targeting the same disease.





**Table of Contents**

***We may not be able to execute our business strategy if we are unable to enter into alliances with other companies that can provide business and scientific capabilities and funds for the development and commercialization of our product candidates. If we are unsuccessful in forming or maintaining these alliances on 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 and collaborators that we believe can provide such capabilities, 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 product 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, sales and distribution. For example, under our collaboration with Medtronic, we are jointly developing ALN-HTT, an RNAi therapeutic for HD, 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 of drugs by infusion device, something that they have never done before with our product candidates. In other alliances, we may expect our collaborators to develop, market and sell certain of our product candidates. We may have limited or no control over the development, sales, marketing and distribution activities of these third parties. Our future revenues may depend heavily on the success of the efforts of these third parties. For example, we are jointly developing and will commercialize certain RNAi products for RSV with Cubist in North America. We will rely entirely on Cubist for the development and commercialization of certain RNAi products for RSV in the rest of the world outside of Asia, where we will rely on Kyowa Hakko Kirin for development and commercialization of any RNAi products for RSV. If Cubist and Kyowa Hakko Kirin are not successful in their commercialization efforts, our future revenues from RNAi therapeutics for RSV may be adversely affected.

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, our ability to successfully demonstrate proof of concept for our technology in man, our ability to demonstrate the safety and efficacy of our specific drug candidates, and the strength of our intellectual property. Even if we do succeed in securing such product alliances, we may not be able to maintain them if, for example, development or approval of a product 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 product candidates and reduce their competitiveness even if they reach the market. Any such delay related to our collaborations could adversely affect our business.

For certain product candidates that we may develop, we have formed collaborations to fund all or part of the costs of drug development and commercialization, such as our collaborations with Novartis, Roche, Takeda, Cubist, Medtronic and NIAID. 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 product candidate, we may not have sufficient funds to develop that or any other product candidate internally, or to bring any product candidates to market. If we do not have sufficient funds to develop and bring our product candidates to market, we will not be able to generate sales revenues from these product candidates, and this will substantially harm our business.

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

Our dependence on collaborators for capabilities and funding means that our business could be adversely affected if any collaborator terminates its collaboration agreement with us or fails to perform its obligations under that agreement. Our current or future collaborations, if any, may not be scientifically or commercially successful. Disputes may arise in the future with respect to the ownership of rights to technology or products developed with collaborators, which could have an adverse effect on our ability to develop and commercialize any affected product candidate.

**Table of Contents**

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 Kirin for the development and commercialization of RSV therapeutics for the treatment of RSV infection in Japan and other major markets in Asia may be terminated by Kyowa Hakko Kirin without cause upon 180-days prior written notice to us, subject to certain conditions, and our agreement with Cubist relating to the development and commercialization of certain RSV therapeutics in territories outside of Asia may be terminated by Cubist at any time upon as little as three months prior written notice, if such notice is given prior to the acceptance for filing of the first application for regulatory approval of a licensed product. If we were to lose a commercialization collaborator, we would have to attract a new collaborator or develop internal sales, distribution and marketing capabilities, which would require us to invest significant amounts of financial and management resources.

In addition, if 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. 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 product candidates could be delayed, curtailed or terminated because we may not have sufficient financial resources or capabilities to continue such development and commercialization on our own.

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

In September 2007, we and Isis formed Regulus, of which we currently own approximately 49%, to discover, develop and commercialize microRNA-based therapeutics. Regulus is exploring therapeutic opportunities that arise from abnormal expression or mutations in microRNAs. Generally, we do not have rights to pursue microRNA-based therapeutics independently of Regulus. If Regulus is unable to discover, develop and commercialize microRNA-based 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' assets, including Regulus' intellectual property and rights to licensed intellectual property. Following the initiation of such a buy-out, we and Isis will mutually determine whether to sell Regulus to us, Isis or a third party. We may not have sufficient funds to buy out Isis' interest in Regulus 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. If Regulus is sold to Isis or a third party, we may lose our rights to participate in the development and commercialization of microRNA-based therapeutics. If we and Isis are unable to negotiate a sale of Regulus, Regulus will distribute and assign its rights, interests and assets to us and Isis in accordance with our percentage interests, except for Regulus' 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-based therapeutics.

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

We rely on independent clinical investigators, contract research organizations and other third-party service providers to assist us in managing, monitoring and otherwise carrying out our clinical trials. We have and we plan to continue to contract with certain third-parties to provide certain services, including site selection, enrollment,

**Table of Contents**

monitoring and data management services. Although we depend heavily on these parties, we do not control them and therefore, we cannot be assured that these third-parties will adequately perform all of their contractual obligations to us. If our third-party service providers cannot adequately fulfill their obligations to us on a timely and satisfactory basis or if the quality and accuracy of our clinical trial data is compromised due to failure to adhere to our protocols or regulatory requirements or if such third-parties otherwise fail to meet deadlines, our development plans may be delayed or terminated.

***We have very limited manufacturing experience or resources and we must incur significant costs to develop this expertise 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-cGMP material for use in *in vitro* and *in vivo* experiments. Some of our product candidates utilize specialized formulations, such as liposomes or LNPs, 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. To fulfill our siRNA requirements, we may also 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 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 product 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.

## **Table of Contents**

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 would have to invest significant financial and management resources to establish these capabilities.***

We have no sales, marketing or distribution experience. We currently expect to rely heavily on third parties to launch and market certain of our product candidates, if approved. However, if we elect to develop internal sales, distribution and marketing capabilities, we will need to invest significant 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.

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

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

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

## **Risks Related to Managing Our Operations**

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

We are highly dependent upon our senior management and scientific staff. The loss of the service of any of the members of our senior management, including Dr. John Maraganore, our Chief Executive Officer, may significantly delay or prevent the achievement of product development and other business objectives. Our employment agreements with our key personnel are terminable without notice. We do not carry key man life insurance on any of our

employees.

Although we have generally been successful in our recruiting efforts, as well as our retention of employees, we face intense competition for qualified individuals from numerous pharmaceutical and biotechnology companies, universities, governmental entities and other research institutions, many of which have substantially greater resources with which to reward qualified individuals than we do. We may be unable to attract and retain suitably qualified individuals, and our failure to do so could have an adverse effect on our ability to implement our business plan.



## **Table of Contents**

*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 December 31, 2009, we had 179 employees in our facility in Cambridge, Massachusetts. Our rapid and substantial growth may place a strain on our administrative and operational infrastructure. If product candidates we develop enter and advance through clinical trials, we will need to expand our development, regulatory, manufacturing, marketing and sales capabilities or contract with other organizations to provide these capabilities for us. 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.

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

Despite the implementation of security measures, our internal computer systems and those of our contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. Such events could cause interruption of our operations. For example, the loss of pre-clinical trial data or data from completed or ongoing clinical trials for our product candidates could result in delays in our regulatory filings and development efforts and significantly increase our costs. To the extent that any disruption or security breach were to result in a loss of or damage to our data, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the development of our product candidates could be delayed.

## **Risks Related to Our Industry**

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

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

Pre-clinical testing and clinical trials of new product candidates are lengthy and expensive and the historical failure rate for product candidates is high. We are developing our most advanced product candidate, ALN-RSV01, for the treatment of RSV infection. In January 2008, we completed our GEMINI study, a Phase II trial designed to evaluate the safety, tolerability and anti-viral activity of ALN-RSV01 in adult subjects experimentally infected with RSV. During 2009, we completed a Phase IIa trial assessing the safety and tolerability of ALN-RSV01 in adult lung transplant patients naturally infected with RSV and we intend to continue the ALN-RSV01 clinical development program for adult lung transplant patients, and pursue jointly with Cubist the development of ALN-RSV02, a second-generation RNAi therapeutic candidate, intended for use in pediatric patients with RSV infection. In February 2010, we initiated a Phase IIb clinical trial to evaluate the clinical efficacy endpoints as well as safety of aerosolized ALN-RSV01 in adult lung transplant patients naturally infected with RSV. The objective of this Phase IIb study is to repeat and extend the clinical results observed in the Phase IIa study. In addition, in March 2009, we initiated a Phase I study of ALN-VSP, our first systemically delivered RNAi therapeutic candidate. We are developing ALN-VSP for the treatment of primary and secondary liver cancer. We have also made regulatory filings to initiate a clinical trial for ALN-TTR01, our second systemically delivered RNAi therapeutic candidate, which targets the TTR gene for the treatment of ATTR. However, we may not be able to further advance these 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 product candidate may not predict the results that will be obtained in subsequent human clinical trials. For

example, ALN-RSV01 may not demonstrate the same results in the Phase IIb study as it did in our Phase IIa trial. In addition, ALN-VSP and our other systemically delivered therapeutic candidates, such as ALN-TTR, employ novel delivery formulations that have yet to be evaluated in human studies and have yet to be proven safe and effective in clinical trials. We, the FDA or other applicable regulatory authorities, or an IRB or

**Table of Contents**

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

Clinical trials of a new product candidate require the enrollment of a sufficient number of patients, including patients who are suffering from the disease the product candidate is intended to treat and who meet other eligibility criteria. Rates of patient enrollment are affected by many factors, including the size of the patient population, the age and condition of the patients, the 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 or difficulties retaining study participants can result in increased costs, longer development times or termination of a clinical trial.

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 or foreign regulatory authorities may decide not to consider any data or information derived from a clinical investigation not subject to initial and continuing IRB review and approval in support of a marketing application.

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

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

- delays in filing INDs or comparable foreign applications or delays or failure in obtaining the necessary approvals from regulators or IRBs in order to commence a clinical trial at a prospective trial site, or their suspension or termination of a clinical trial once commenced;

- conditions imposed on us by the FDA or comparable foreign authorities regarding the scope or design of our clinical trials;

- problems in engaging IRBs to oversee trials or problems in obtaining or maintaining IRB approval of trials;

- delays in enrolling patients and volunteers into clinical trials, and variability in the number and types of patients and volunteers available for clinical trials;

- high drop-out rates for patients and volunteers in clinical trials;

- negative or inconclusive results from our clinical trials or the clinical trials of others for product candidates similar to ours;

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

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

poor effectiveness of our product candidates during clinical trials;

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

failure of our third party contractors or investigators to comply with regulatory requirements or otherwise meet their contractual obligations in a timely manner, or at all;

**Table of Contents**

governmental or regulatory delays and changes in regulatory requirements, policy and guidelines, including the imposition of additional regulatory oversight around clinical testing generally or with respect to our technology in particular; or

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

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

***The regulatory approval process may be delayed for any products we develop that require the use of specialized drug delivery devices, which may require us to incur additional costs and delay receipt of any potential product revenue.***

Some product 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 HD, Parkinson's disease 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 collaborations 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 diseased parts of the body, 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 product 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 product candidates.***

Our product candidates are subject to extensive governmental regulations relating to, among other things, research, testing, development, manufacturing, safety, efficacy, recordkeeping, labeling, storage, marketing and distribution of drugs. Rigorous pre-clinical testing and clinical trials and an extensive regulatory approval process are required to be successfully completed in the United States and in many foreign jurisdictions before a new drug can be marketed. Satisfaction of these and other regulatory requirements is costly, time consuming, uncertain and subject to unanticipated delays. It is possible that none of the product candidates we may develop will obtain the regulatory approvals necessary for us or our collaborators to begin selling them.

We have 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 type, complexity and novelty of the product candidate. The standards that the FDA and its foreign counterparts use when regulating us are

not always applied predictably or uniformly and can change. Any analysis we perform of data from pre-clinical and clinical activities is subject to confirmation and interpretation by regulatory authorities, which could delay, limit or prevent regulatory approval. We may also encounter unexpected delays or increased costs due to new government regulations, for example, from future legislation or administrative action, or from changes in FDA policy during the period of product development, clinical trials and FDA regulatory review. It is impossible to predict whether legislative changes will be enacted, or whether FDA or foreign regulations, guidance or interpretations will be changed, or what the impact of such changes, if any, may be.

**Table of Contents**

Because the drugs we are intending to develop may represent a new class of drug, the FDA and its foreign counterparts have not yet established any definitive policies, practices or guidelines in relation to these drugs. While the product candidates that we are currently developing are regulated as new drugs 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 product candidate for which we are seeking approval. Furthermore, any regulatory approval to market a product may be subject to limitations on the approved indicated uses for which we may market the product or the labeling or other restrictions. These limitations and restrictions may limit the size of the market for the product and affect reimbursement by third-party payors.

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

Before obtaining regulatory approval for the sale of our product candidates, we must conduct, at our own expense, extensive pre-clinical tests and clinical trials to demonstrate the safety and efficacy in humans of our product candidates. Pre-clinical and clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. 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 product 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 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, or at all;

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, failure to achieve established success criteria, or if, in their opinion, the participants are being exposed to unacceptable health risks;



**Table of Contents**

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

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

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

effects of our product 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 be subject to other penalties, and our business would be seriously harmed.***

Following any initial regulatory approval of any drugs we may develop, we will also be subject to continuing regulatory review, including the review of adverse drug experiences and clinical results that are reported after our drug products are made commercially available. This would include results from any post-marketing tests or surveillance to monitor the safety and efficacy of the drug product required as a condition of approval. Any regulatory approvals that we receive for our product candidates may also be subject to limitations on the approved indicated uses for which the product may be marketed. Other ongoing regulatory requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with cGMP requirements and GCP for any clinical trials that we conduct post-approval. In addition, we intend to conduct clinical trials for our product candidates, and to seek approval to market our product candidates, in jurisdictions outside of the United States, and therefore will be subject to, and must comply with, regulatory requirements in those jurisdictions.

The manufacturer and manufacturing facilities we use to make any of our product candidates will also be subject to periodic review and inspection by the FDA and other regulatory agencies. The discovery of any new or previously unknown problems with the product, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers, manufacturing processes or facilities, 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 or our collaborators, manufacturers or service providers fail to comply with applicable continuing regulatory requirements in the United States or foreign jurisdictions in which we may seek to market our products, we or they may be subject to, among other things, fines, warning letters, holds on clinical trials, refusal by the FDA to approve pending applications or supplements to approved applications, suspension or withdrawal of regulatory approval, product recalls and seizures, refusal to permit the import or export of products, operating restrictions, civil penalties and criminal prosecution.

***Even if we receive regulatory approval to market our product candidates, the market may not be receptive to our product candidates upon their commercial introduction, which will prevent us from becoming profitable.***

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

**Table of Contents**

Other factors that we believe will materially affect market acceptance of our product candidates include:

the timing of our receipt of any marketing approvals, the terms of any approvals and the countries in which approvals are obtained;

the safety and efficacy of our product candidates, as demonstrated in clinical trials;

relative convenience and ease of administration of our product candidates;

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

the success of our physician education programs;

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

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

availability of alternative effective treatments for the diseases that product candidates we develop are intended to treat and the relative risks, benefits and costs of the treatments.

***Even if we develop an RNAi therapeutic product for the prevention or treatment of infection by hemorrhagic fever viruses such as Ebola, governments may not elect to purchase such a product, 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. 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 believe 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. In addition, government contractors and subcontractors are generally subject to contractual and regulatory requirements that differ from typical commercial business arrangements. These requirements may make it more costly for us to serve government customers and may expose us to legal and regulatory liability risks that would not arise in sales to non-governmental customers.

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

As a manufacturer of pharmaceuticals, we are subject to federal, state, and foreign health care laws and regulations pertaining to fraud and abuse and patients' rights. These laws and regulations include:

The U.S. federal health care program anti-kickback law, which prohibits, among other things, persons from soliciting, receiving or providing remuneration, directly or indirectly, to induce either the referral of an individual for a healthcare item or service, or the purchasing or ordering of an item or service, for which

payment may be made under a federal healthcare program such as Medicare or Medicaid;

The U.S. federal false claims law, which prohibits, among other things, individuals or entities from knowingly presenting or causing to be presented, claims for payment by government funded programs such as Medicare or Medicaid that are false or fraudulent, and which may apply to us by virtue of statements and representations made to customers or third parties;

The U.S. federal Health Insurance Portability and Accountability Act, or HIPAA, and Health Information Technology for Economic and Clinical Health, or HITECH, Act, which prohibit executing a scheme to defraud health care programs; impose requirements relating to the privacy, security, and transmission of

**Table of Contents**

individually identifiable health information; and require notification to affected individuals and regulatory authorities of certain breaches of security of individually identifiable health information; and

State laws comparable to each of the above federal laws, such as, for example, anti-kickback and false claims laws applicable to commercial insurers and other non-federal payors, requirements for mandatory corporate regulatory compliance programs, and laws relating to patient data privacy and security.

If our operations are found to be in violation of any such requirements, we may be subject to penalties, including civil or criminal penalties, monetary damages, the curtailment or restructuring of our operations, loss of eligibility to obtain approvals from the FDA, or exclusion from participation in government contracting or other government programs, any of which could adversely affect our financial results. Although effective compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, these risks cannot be entirely eliminated. Any action against us for an alleged or suspected violation could cause us to incur significant legal expenses and could divert our management's attention from the operation of our business, even if our defense is successful. In addition, achieving and sustaining compliance with applicable laws and regulations may be costly to us in terms of money, time and resources.

If we or our collaborators, manufacturers or service providers fail to comply with applicable federal, state or foreign laws or regulations, we could be subject to enforcement actions, which could affect our ability to develop, market and sell our products successfully and could harm our reputation and lead to reduced acceptance of our products by the market. These enforcement actions include, among others:

warning letters;

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

restrictions on, or prohibitions against, marketing our products;

restrictions on, or prohibitions against, importation or exportation of our products;

suspension of review or refusal to approve pending applications or supplements to approved applications;

exclusion from participation in government-funded healthcare programs;

exclusion from eligibility for the award of government contracts for our products;

suspension or withdrawal of product approvals;

product seizures;

injunctions; and

civil and criminal penalties and fines.

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

The regulations that govern marketing approvals, pricing and reimbursement for new drugs vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. Although we intend to monitor these regulations, 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

**Table of Contents**

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 standards 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 and for which we obtain regulatory approval could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products, and our overall financial condition.

We believe that the efforts of governments and third-party payors to contain or reduce the cost of healthcare and legislative and regulatory proposals to broaden the availability of healthcare will continue to affect the business and financial condition of pharmaceutical and biopharmaceutical companies. A number of legislative and regulatory changes in the healthcare system in the United States and other major healthcare markets have been proposed in recent years, and such efforts have expanded substantially in the last year. These developments have included prescription drug benefit legislation that was enacted and took effect in January 2006, healthcare reform legislation recently enacted by certain states, and major health care reform legislation that is currently pending in Congress. Many such proposals could, directly or indirectly, affect our ability to sell our products, if approved, at a favorable price. We cannot predict the initiatives that may be adopted in the future. Further federal and state legislative and regulatory developments are likely and we expect ongoing initiatives in the United States to increase pressure on drug pricing. Such reforms could have an adverse effect on anticipated revenues from product candidates that we may successfully develop and for which we may obtain regulatory approval and may affect our overall financial condition and ability to develop drug candidates.

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

Our business exposes us to significant potential product liability risks that are inherent in the development, testing, manufacturing and marketing of human therapeutic products. Product liability claims could delay or prevent completion of our clinical development programs. If we succeed in marketing products, such claims could



## **Table of Contents**

result in an FDA investigation of the safety and effectiveness of our products, our manufacturing processes and facilities or our marketing programs, and potentially a recall of our products or more serious enforcement action, limitations on the approved indications for which they may be used, or suspension or withdrawal of approvals. Regardless of the merits or eventual outcome, liability claims may also result in injury to our reputation, costs to defend the related litigation, a diversion of management's time and our resources, and substantial monetary awards to trial participants or patients. We currently have product liability insurance that we believe is appropriate for our stage of development and may need to obtain higher levels prior to marketing any of our product candidates. Any insurance we have or may obtain may not provide sufficient coverage against potential liabilities. Furthermore, clinical trial and product liability insurance is becoming increasingly expensive. As a result, we may be unable to obtain sufficient insurance at a reasonable cost to protect us against losses caused by product liability claims that could have a material adverse effect on our business.

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

Our research 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 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. 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 third-party collaborators to file patent applications relating to proprietary technology that

## **Table of Contents**

we develop jointly during certain collaborations. The process of obtaining patent protection is expensive and time-consuming. If our present or future collaborators fail to file and prosecute all necessary and desirable patent applications at a reasonable cost and in a timely manner, our business will be adversely affected. Despite our efforts and the efforts of our collaborators to protect our proprietary rights, unauthorized parties may be able to obtain and use information that we regard as proprietary. While issued patents are presumed valid, this does not guarantee that the patent will survive a validity challenge or be held enforceable. Any patents we have obtained, or obtain in the future, may be challenged, invalidated, adjudged unenforceable or circumvented by parties attempting to design around our intellectual property. Moreover, third parties or the 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. In addition, there are periodic discussions in the Congress of the United States and in international jurisdictions about modifying various aspects of patent law. If any such changes are enacted and do not provide adequate protection for discoveries, including our ability to pursue infringers of our patents for substantial damages, our business could be adversely affected. There is also no uniform, worldwide policy regarding the subject matter and scope of claims granted or allowable in pharmaceutical or biotechnology patents. Accordingly, we do not know the degree of future protection for our proprietary rights or the breadth of claims that will be allowed in any patents issued to us or to others.

We also rely to a certain extent on trade secrets, know-how and technology, which are not protected by patents, to maintain our competitive position. If any trade secret, know-how or other technology not protected by a patent were to be disclosed to or independently developed by a competitor, our business and financial condition could be materially adversely affected.

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

We are a party to a number of licenses that give us rights to third party intellectual property that is necessary or useful for our business. In particular, we have obtained licenses from, among others, Cancer Research Technology Limited, Isis, MIT, Whitehead, Max Planck, Stanford University, Tekmira and UTSW. We also intend to enter into additional licenses to third party intellectual property in the future.

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

In June 2009, we joined with Max Planck in taking legal action against Whitehead, MIT and UMass. The complaint, initially filed in Suffolk County Superior Court in Boston, Massachusetts and subsequently removed to the

U.S. District Court for the District of Massachusetts, alleges, among other things, that the defendants have improperly prosecuted the Tuschl I patent applications and wrongfully incorporated inventions covered by the Tuschl II patent applications into the Tuschl I patent applications, thereby potentially damaging the value of inventions reflected in the Tuschl I and Tuschl II patent applications. In the field of RNAi therapeutics, we are the

**Table of Contents**

exclusive licensee of the Tuschl I patent applications from Max Planck, MIT and Whitehead and of the Tuschl II patent applications from Max Planck.

The complaint seeks to enjoin the defendants from taking any further action in connection with the prosecution of any Tuschl I application, a declaratory judgment and unspecified monetary damages. In August 2009, the court denied our motion for a preliminary injunction. In addition, in August 2009, Whitehead and UMass filed counterclaims against us and Max Planck, including for breach of contract. A trial on the merits was originally scheduled to begin in February 2010. In January 2010, we and Max Planck filed a motion for leave to file an amended complaint expanding upon the allegations in the original complaint. In January 2010, the court granted this motion allowing our amended complaint and postponed the start of the trial. We currently expect the trial to start in June 2010.

In addition, in September 2009, the USPTO granted Max Planck's petition to revoke power of attorney in connection with the prosecution of the Tuschl I patent application. This action prevents the defendants from filing any papers with the USPTO in connection with further prosecution of the Tuschl I patent application without the agreement of Max Planck. Whitehead's petition to overturn the ruling on Max Planck's petition was denied.

Although we, along with Max Planck, are vigorously asserting our rights in this case, litigation is subject to inherent uncertainty and a court could ultimately rule against us. In addition, litigation is costly and may divert the attention of our management and other resources that would otherwise be engaged in running our business.

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

RNAi is a relatively new scientific field, the commercial exploitation of which has resulted in many different patents and patent applications from organizations and individuals seeking to obtain patent protection in the field. We have obtained grants and issuances of RNAi patents and have licensed many of these patents from third parties on an exclusive basis. The issued patents and pending patent applications in the United States and in key markets around the world that we own or license claim many different methods, compositions and processes relating to the discovery, development, manufacture and commercialization of RNAi therapeutics. Specifically, we have a portfolio of patents, patent applications and other intellectual property covering: fundamental aspects of the structure and uses of siRNAs, including their manufacture and use as therapeutics, and RNAi-related mechanisms; chemical modifications to siRNAs that improve their suitability for therapeutic uses; siRNAs directed to specific targets as treatments for particular diseases; and delivery technologies, such as in the field of cationic liposomes.

As the field of RNAi therapeutics is maturing, patent applications are being fully processed by national patent offices around the world. There is uncertainty about which patents will issue, and, if they do, as to when, to whom, and with what claims. It is likely that there will be significant litigation and other proceedings, such as interference, reexamination and opposition proceedings, in various patent offices relating to patent rights in the RNAi field. For example, various third parties have initiated oppositions to patents in our Kreutzer-Limmer and Tuschl II series in the EPO and in other jurisdictions. We expect that additional oppositions will be filed in the EPO and elsewhere, and other challenges will be raised relating to other patents and patent applications in our portfolio. In many cases, the possibility of appeal exists for either us or our opponents, and it may be years before final, unappealable rulings are made with respect to these patents in certain jurisdictions. The timing and outcome of these and other proceedings is uncertain and may adversely affect our business if we are not successful in defending the patentability and scope of our pending and issued patent claims. In addition, third parties may attempt to invalidate our intellectual property rights. Even if our rights are not directly challenged, disputes could lead to the weakening of our intellectual property rights. Our defense against any attempt by third parties to circumvent or invalidate our intellectual property rights could be costly to us, could require significant time and attention of our management and could have a material adverse effect on our business and our ability to successfully compete in the field of RNAi.

There are many issued and pending patents that claim aspects of oligonucleotide chemistry that we may need to apply to our siRNA therapeutic candidates. There are also many issued patents that claim targeting genes or portions of genes that may be relevant for siRNA drugs we wish to develop. Thus, it is possible that one or more

**Table of Contents**

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.

***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



## **Table of Contents**

secret rights against such party. Costly and time-consuming litigation could be necessary to enforce and determine the scope of our proprietary rights, and failure to obtain or maintain trade secret protection could adversely affect our competitive business position.

### **Risks Related to Competition**

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

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

- much greater financial, technical and human resources than we have at every stage of the discovery, development, manufacture and commercialization of products;

- more extensive experience in pre-clinical testing, conducting clinical trials, obtaining regulatory approvals, and in manufacturing, marketing and selling 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 cancers, ATTR, 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 product candidates, and obtain approval for them, we will face competition based on many different factors, including:

- the safety and effectiveness of our products;

- the ease with which our products can be administered and the extent to which patients accept relatively new routes of administration;

- the timing and scope of regulatory approvals for these products;

- the availability and cost of manufacturing, marketing and sales capabilities;

price;

reimbursement coverage; and

patent position.

Our competitors may develop or commercialize products with significant advantages over any products we develop based on any of the factors listed above or on other factors. Our competitors may therefore be more successful in commercializing their products than we are, which could adversely affect our competitive position and business. Competitive products may make any products we develop obsolete or noncompetitive before we can recover the expenses of developing and commercializing our product candidates. Such competitors could also

## **Table of Contents**

recruit our employees, which could negatively impact our level of expertise and the ability to execute on our business plan. Furthermore, we also face competition from existing and new treatment methods that reduce or eliminate the need for drugs, such as the use of advanced medical devices. The development of new medical devices or other treatment methods for the diseases we are targeting could make our product candidates noncompetitive, obsolete or uneconomical.

***We face competition from other companies that are working to develop novel drugs 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 multiple companies that are working in the field of RNAi. In addition, we granted licenses or options for licenses to Isis, GeneCare, Benitec, Calando, Tekmira, Quark 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 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 therapeutics, antisense drugs target mRNAs in order to suppress the activity of specific genes. Isis is currently marketing an antisense drug and has several antisense product candidates in clinical trials. 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.

**Table of Contents**

***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 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 December 31, 2009, Novartis held 13.3% 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.

**Table of Contents**

**ITEM 1B. UNRESOLVED STAFF COMMENTS**

Not applicable.

**ITEM 2. PROPERTIES**

Our operations are based primarily in Cambridge, Massachusetts. As of January 31, 2010, we lease approximately 95,000 square feet of office and laboratory space in Cambridge, Massachusetts. The lease for this property expires in September 2016. We believe that the total space available to us under our current lease will meet our needs for the foreseeable future and that additional space would be available to us on commercially reasonable terms if required.

**ITEM 3. LEGAL PROCEEDINGS**

In June 2009, we joined with Max Planck in taking legal action against Whitehead, MIT and UMass. The complaint, initially filed in Suffolk County Superior Court in Boston, Massachusetts and subsequently removed to the U.S. District Court for the District of Massachusetts, alleges, among other things, that the defendants have improperly prosecuted the Tuschl I patent applications and wrongfully incorporated inventions covered by the Tuschl II patent applications into the Tuschl I patent applications, thereby potentially damaging the value of inventions reflected in the Tuschl I and Tuschl II patent applications. In the field of RNAi therapeutics, we are the exclusive licensee of the Tuschl I patent applications from Max Planck, MIT and Whitehead and of the Tuschl II patent applications from Max Planck.

The complaint seeks to enjoin the defendants from taking any further action in connection with the prosecution of any Tuschl I application, a declaratory judgment and unspecified monetary damages. In August 2009, the court denied our motion for a preliminary injunction. In addition, in August 2009, Whitehead and UMass filed counterclaims against us and Max Planck, including for breach of contract. A trial on the merits was originally scheduled to begin in February 2010. In January 2010, we and Max Planck filed a motion for leave to file an amended complaint expanding upon the allegations in the original complaint. In January 2010, the court granted this motion allowing our amended complaint and postponed the start of the trial. We currently expect the trial to start in June 2010.

In addition, in September 2009, the USPTO granted Max Planck's petition to revoke power of attorney in connection with the prosecution of the Tuschl I patent application. This action prevents the defendants from filing any papers with the USPTO in connection with further prosecution of the Tuschl I patent application without the agreement of Max Planck. Whitehead's petition to overturn the ruling on Max Planck's petition was denied.

Although we, along with Max Planck, are vigorously asserting our rights in this case, litigation is subject to inherent uncertainty and a court could ultimately rule against us. In addition, litigation is costly and may divert the attention of our management and other resources that would otherwise be engaged in running our business.

**ITEM 4. SUBMISSION OF MATTERS TO A VOTE OF SECURITY HOLDERS**

No matters were submitted to a vote of our security holders during the fourth quarter of the fiscal year ended December 31, 2009.

**Table of Contents****PART II****ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES****Market Information**

Our common stock began trading on The NASDAQ Global Market on May 28, 2004 under the symbol ALNY. Prior to that time, there was no established public trading market for our common stock. The following table sets forth the high and low sale prices per share for our common stock on The NASDAQ Global Market for the periods indicated:

<b>Year Ended December 31, 2008:</b>	<b>High</b>	<b>Low</b>
First Quarter	\$ 35.19	\$ 22.25
Second Quarter	\$ 30.74	\$ 22.55
Third Quarter	\$ 36.37	\$ 25.07
Fourth Quarter	\$ 28.95	\$ 16.37

<b>Year Ended December 31, 2009:</b>	<b>High</b>	<b>Low</b>
First Quarter	\$ 26.36	\$ 14.82
Second Quarter	\$ 23.10	\$ 16.29
Third Quarter	\$ 24.75	\$ 19.00
Fourth Quarter	\$ 22.87	\$ 15.45

**Holders of record**

As of January 31, 2010, there were approximately 52 holders of record of our common stock. Because many of our shares are held by brokers and other institutions on behalf of stockholders, we are unable to estimate the total number of individual stockholders represented by these record holders.

**Dividends**

We have never paid or declared any cash dividends on our common stock. We currently intend to retain any earnings for future growth and, therefore, do not expect to pay cash dividends in the foreseeable future.

**Securities Authorized for Issuance Under Equity Compensation Plans**

We will file with the SEC a definitive Proxy Statement, which we refer to herein as the Proxy Statement, not later than 120 days after the close of the fiscal year ended December 31, 2009. The information required by this item relating to our equity compensation plans is incorporated herein by reference to the information contained under the section captioned "Equity Compensation Plan Information" of the Proxy Statement.



**Table of Contents****Stock Performance Graph**

*The following performance graph and related information shall not be deemed soliciting material or to be filed with the SEC, nor shall such information be incorporated by reference into any future filing under the Securities Act of 1933 or Securities Exchange Act of 1934, each as amended, except to the extent that we specifically incorporate it by reference into such filing.*

The comparative stock performance graph below compares the five-year cumulative total stockholder return (assuming reinvestment of dividends, if any) from investing \$100 on December 31, 2004, to the close of the last trading day of 2009, in each of (i) our common stock, (ii) the NASDAQ Stock Market (U.S.) Index and (iii) the NASDAQ Pharmaceutical Index. The stock price performance reflected in the graph below is not necessarily indicative of future price performance.

**Comparison of Five-Year Cumulative Total Return  
Among Alnylam Pharmaceuticals, Inc.,  
NASDAQ Stock Market (U.S.) Index and NASDAQ Pharmaceuticals Index**

	<b>12/31/2004</b>	<b>12/30/2005</b>	<b>12/29/2006</b>	<b>12/31/2007</b>	<b>12/31/2008</b>	<b>12/31/2009</b>
Alnylam Pharmaceuticals, Inc.	\$ 100.00	\$ 178.85	\$ 286.48	\$ 389.29	\$ 331.06	\$ 235.88
Nasdaq Stock Market (U.S.) Index	\$ 100.00	\$ 102.13	\$ 112.19	\$ 121.68	\$ 58.64	\$ 84.28
Nasdaq Pharmaceutical Index	\$ 100.00	\$ 110.12	\$ 107.79	\$ 113.36	\$ 105.48	\$ 118.52

**Table of Contents****ITEM 6. SELECTED CONSOLIDATED FINANCIAL DATA**

The following selected consolidated financial data for each of the five years in the period ended December 31, 2009 are derived from our audited consolidated financial statements. The selected consolidated financial data set forth below should be read in conjunction with Management's Discussion and Analysis of Financial Condition and Results of Operations and the financial statements, and the related Notes, included elsewhere in this annual report on Form 10-K. Historical results are not necessarily indicative of future results.

**Selected Consolidated Financial Data**  
(In thousands, except per share data)

	<b>Year Ended December 31,</b>				
	<b>2009</b>	<b>2008</b>	<b>2007</b>	<b>2006</b>	<b>2005</b>
<b>Statement of Operations Data:</b>					
Net revenues from research collaborators	\$ 100,533	\$ 96,163	\$ 50,897	\$ 26,930	\$ 5,716
Operating expenses(1)	148,644	123,998	144,074	66,431	49,188
Loss from operations	(48,111)	(27,835)	(93,177)	(39,501)	(43,472)
Net loss	(47,590)	(26,249)	(85,466)	(34,608)	(42,914)
Net loss per common share - basic and diluted	\$ (1.14)	\$ (0.64)	\$ (2.21)	\$ (1.09)	\$ (1.96)
Weighted average common shares outstanding - basic and diluted	41,633	41,077	38,657	31,890	21,949
(1) Non-cash stock-based compensation expenses included in operating expenses	\$ 19,727	\$ 16,382	\$ 14,472	\$ 8,304	\$ 4,597

	<b>December 31,</b>				
	<b>2009</b>	<b>2008</b>	<b>2007</b>	<b>2006</b>	<b>2005</b>
<b>Balance Sheet Data:</b>					
Cash, cash equivalents and marketable securities	\$ 435,316	\$ 512,709	\$ 455,602	\$ 217,260	\$ 80,002
Working capital	182,801	343,672	314,427	199,859	63,930
Total assets	481,385	554,676	493,791	240,006	98,348
Notes payable			6,758	9,136	7,395
Total stockholders' equity	177,965	202,125	199,168	201,174	61,779

**Table of Contents**

**ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS**

**Overview**

We are a biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. RNAi is a naturally occurring biological pathway within cells for selectively silencing and regulating the expression of specific genes. Since many diseases are caused by the inappropriate activity of specific genes, the ability to silence genes selectively through RNAi could provide a new way to treat a wide range of human diseases. We believe that drugs that work through RNAi have the potential to become a broad new class of drugs, like small molecule, protein and antibody drugs. Using our intellectual property and the expertise we have built in RNAi, we are developing a set of biological and chemical methods and know-how that we apply in a systematic way to develop RNAi therapeutics for a variety of diseases.

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. We are working to develop RNAi therapeutics that are delivered directly to specific sites of disease, as well as RNAi therapeutics that are administered systemically through the bloodstream by intravenous, subcutaneous or intramuscular approaches. 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. In February 2008, we reported positive results from our Phase II experimental RSV infection clinical trial, referred to as the GEMINI study. In July 2009, we and Cubist Pharmaceuticals, Inc., or Cubist, reported results from a Phase IIa clinical trial assessing the safety and tolerability of aerosolized ALN-RSV01 versus placebo in adult lung transplant patients naturally infected with RSV. In February 2010, we initiated a multi-center, global, randomized, double-blind, placebo-controlled Phase IIb clinical trial to evaluate the clinical efficacy endpoints, as well as safety of aerosolized ALN-RSV01 in adult lung transplant patients naturally infected with RSV.

We have formed collaborations with Cubist and Kyowa Hakko Kirin Co., Ltd., or Kyowa Hakko Kirin, for the development and commercialization of RNAi products for RSV. We have an agreement to jointly develop and commercialize certain RNAi products for RSV with Cubist in North America. Cubist has responsibility for developing and commercializing any such products in the rest of the world outside of Asia, and Kyowa Hakko Kirin has the responsibility for developing and commercializing any RNAi products for RSV in Asia. In November 2009, we and Cubist agreed that Alnylam would move forward with the development of ALN-RSV01, and together we would focus our collaboration and joint development efforts on ALN-RSV02, a second-generation compound, intended for use in pediatric patients. We and Cubist each bears one-half of the related development costs for ALN-RSV02. We are also continuing to develop ALN-RSV01 for adult transplant patients at our sole discretion and expense. Cubist has the right to resume the collaboration on ALN-RSV01 in the future, which right may be exercised for a specified period of time following the completion of our Phase IIb trial of ALN-RSV01, subject to the payment by Cubist of an opt-in fee representing reimbursement of an agreed upon percentage of certain of our development expenses for ALN-RSV01.

In March 2009, we initiated a Phase I study for ALN-VSP, our second clinical program and our first systemically delivered RNAi therapeutic candidate. We are developing ALN-VSP for the treatment of liver cancers, including hepatocellular carcinoma, or HCC, and other solid tumors with liver involvement. The Phase I study is a multi-center, open label, dose escalation study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of intravenous ALN-VSP in up to approximately 55 patients with advanced solid tumors with liver involvement, including HCC.

In December 2009, we filed regulatory applications to initiate a clinical trial for ALN-TTR01, our second systemically delivered RNAi therapeutic candidate. We are developing ALN-TTR, which targets the transthyretin, or TTR, gene, for the treatment of TTR-mediated amyloidosis, or ATTR. We plan to initiate a Phase I trial of ALN-TTR01 in ATTR patients in the first half of 2010. ALN-TTR01 employs a first generation lipid nanoparticle, or LNP, formulation. In parallel, we are also advancing ALN-TTR02 utilizing second-generation LNPs.

**Table of Contents**

In January 2010, we announced that we expect ALN-PCS, a systemically delivered RNAi therapeutic candidate for the treatment of hypercholesterolemia, to be our next clinical candidate. ALN-PCS targets a gene called proprotein convertase subtilisin/kexin type 9, or PCSK9.

We are also working on a number of programs in pre-clinical development, including ALN-HTT, an RNAi therapeutic candidate targeting the huntingtin gene, for the treatment of Huntington's disease, or HD, which we are developing in collaboration with Medtronic, Inc., or Medtronic. We have additional discovery programs for RNAi therapeutics for the treatment of a broad range of diseases.

In addition, we are working internally and with third-party collaborators to develop capabilities to deliver our RNAi therapeutics directly to specific sites of disease, such as the delivery of ALN-RSV to the lungs. We are also working to extend our capabilities to advance the development of RNAi therapeutics that are administered systemically by intravenous, subcutaneous or intramuscular approaches. Over the past 12 to 18 months, we have made several of what we believe to be major advances relating to the delivery of RNAi therapeutics, both internally and together with our collaborators. We have numerous RNAi therapeutic delivery collaborations and intend to continue to collaborate with government, academic and corporate third parties to evaluate different delivery options.

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 as well as those claiming crucial chemical modifications and promising delivery technologies. We believe that no other company possesses a portfolio of such broad and exclusive rights to the patents and patent applications required for the commercialization of RNAi therapeutics. Given the importance of our intellectual property portfolio to our business operations, we intend to vigorously enforce our rights and defend against challenges that have arisen or may arise in this area.

In addition, our expertise in RNAi therapeutics and broad intellectual property estate have allowed us to form alliances with leading companies, including Isis Pharmaceuticals, Inc., or Isis, Medtronic, Novartis Pharma AG, or Novartis, Biogen Idec Inc., or Biogen Idec, F. Hoffmann-La Roche Ltd, or Roche, Takeda Pharmaceutical Company Limited, or Takeda, Kyowa Hakko Kirin and Cubist. We have also entered into contracts with government agencies, including the National Institute of Allergy and Infectious Diseases, or NIAID, a component of the National Institutes of Health, or NIH. We have established collaborations with and, in some instances, received funding from major medical and disease associations. Finally, to further enable the field and monetize our intellectual property rights, we also grant licenses to biotechnology companies for the development and commercialization of RNAi therapeutics for specified targets in which we have no direct strategic interest under our InterfeRx™ program and to research companies that commercialize RNAi reagents or services under our research product licenses.

We also seek opportunities to form new ventures in areas outside our core strategic focus. For example, during 2009, we presented new data regarding the application of RNAi technology to improve the manufacturing processes for biologics, which is comprised of recombinant proteins, monoclonal antibodies and vaccines. This initiative, which we are advancing in an internal effort referred to as Alnylam Biotherapeutics, has the potential to create new business opportunities. Additionally, in 2007, we and Isis established Regulus Therapeutics Inc., formerly Regulus Therapeutics LLC, or Regulus, a company focused on the discovery, development and commercialization of microRNA-based therapeutics. Because microRNAs are believed to regulate whole networks of genes that can be involved in discrete disease processes, microRNA-based therapeutics represent a possible new approach to target the pathways of human disease. Given the broad applications for RNAi technology, we believe additional opportunities exist for new ventures.

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 December 31, 2009, we had an accumulated deficit of \$299.8 million. Through December 31, 2009, 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 December 31, 2009, a substantial portion of our total net revenues have been collaboration revenues derived from our strategic alliances with Roche,

**Table of Contents**

Takeda and Novartis, 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 due primarily 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 and is in Phase II clinical studies. In March 2009, we initiated a Phase I study for ALN-VSP, our second clinical program and our first systemically delivered RNAi therapeutic candidate for the treatment of primary and secondary liver cancer. In December 2009, we filed regulatory applications to initiate a clinical trial for ALN-TTR01, our second systemically delivered RNAi therapeutic candidate. We are developing ALN-TTR, which targets the TTR gene, for the treatment of ATTR. We plan to initiate a Phase I trial of ALN-TTR01 in ATTR patients in the first half of 2010. ALN-TTR01 employs a first generation LNP formulation. In parallel, we are also advancing ALN-TTR02 utilizing second-generation LNPs. In January 2010, we announced that we expect ALN-PCS, a systemically delivered RNAi therapeutic candidate for the treatment of hypercholesterolemia, to be our next clinical candidate. We also have a development program focused on the treatment of HD. In addition, we 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, Parkinson's disease, progressive multifocal leukoencephalopathy, or PML, and other undisclosed programs, as well as several other diseases that are the subject of our strategic alliances. 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 government, 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;



**Table of Contents**

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

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

the cost and timing of establishing sufficient clinical and commercial supplies 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 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 I, Item 1A of this annual report on Form 10-K 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, capabilities, technical resources and intellectual property to further our development efforts and to generate revenues. 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 partnerships on specific RNAi therapeutic programs. We have entered into broad, non-exclusive platform license agreements with Roche and Takeda, under which we are also collaborating with each of Roche and Takeda on RNAi drug discovery for one or more disease targets. We are pursuing 50-50 co-development programs with Cubist and Medtronic for the development and commercialization of ALN-RSV02 and ALN-HTT, respectively. In addition, we have entered into a product alliance with Kyowa Hakko Kirin for the development and commercialization of ALN-RSV in territories not covered by the Cubist agreement, which include Japan and other markets in Asia. We also have discovery and development alliances with Isis, Novartis and Biogen Idec.

We also seek opportunities to form new ventures in areas outside our core strategic focus. For example, during 2009, we established Alnylam Biotherapeutics, an internal effort regarding the application of RNAi technology to improve the manufacturing processes for biologics, an approach that has the potential to create new business opportunities. This initiative is focused on applying RNAi technologies to the biologics marketplace, which is comprised of recombinant proteins, monoclonal antibodies, and vaccines. In addition, during 2007, we formed Regulus, together with Isis, to capitalize on our technology and intellectual property in the field of microRNA-based therapeutics. Given the broad applications for RNAi technology, we believe additional opportunities exist for new ventures.

To generate revenues from our intellectual property rights, we grant licenses to biotechnology companies under our InterfeRx program for the development and commercialization of RNAi therapeutics for specified targets in which we have no direct strategic interest. We also license key aspects of our intellectual property to companies active in the research products and services market, which includes the manufacture and sale of reagents. Our InterfeRx and research product licenses aim to generate modest near-term revenues that we can re-invest in the development of our proprietary RNAi therapeutics pipeline. As of January 31, 2010, we had granted such licenses, on both an exclusive and non-exclusive basis, to approximately 20 companies.

Since delivery of RNAi therapeutics remains a major objective of our research activities, we also look to form collaboration and licensing agreements with other companies and academic institutions to gain access to delivery technologies. For example, we have entered into agreements with Tekmira Pharmaceuticals Corporation, or Tekmira, the Massachusetts Institute of Technology, or MIT, The University of British Columbia, or UBC, and AICana Technologies, Inc., or AICana, among others, to focus on various delivery strategies. We have also entered into license agreements with Isis, Max Planck Innovation GmbH, Tekmira and MIT, as well as a number of other entities, to obtain rights to important intellectual property in the field of RNAi. In April 2009, we established a new collaboration with Isis focused on the development of single-stranded RNAi, or ssRNAi, technology.

## **Table of Contents**

Additionally, we seek funding for the development of our proprietary RNAi therapeutics pipeline from the government and foundations. In 2006, NIAID awarded us a contract to advance the development of a broad spectrum RNAi anti-viral therapeutic against hemorrhagic fever virus, including the Ebola virus. In 2007, the Defense Threat Reduction Agency, or DTRA, an agency of the United States Department of Defense, awarded us a contract to advance the development of a broad spectrum RNAi anti-viral therapeutic for hemorrhagic fever virus, which contract ended in February 2009. In addition, we have obtained funding for pre-clinical discovery programs from organizations such as The Michael J. Fox Foundation.

In September 2007, we terminated our amended and restated research collaboration and license agreement with Merck & Co., Inc., or Merck. Pursuant to the termination agreement, all license grants of intellectual property to develop, manufacture and/or commercialize RNAi therapeutic products under the amended and restated research collaboration and license agreement ceased as of the date of the termination agreement, subject to certain specified exceptions. The termination agreement further provides that, subject to certain conditions, we and Merck will each retain sole ownership and rights in our own intellectual property.

### **Platform Alliances.**

**Roche.** In July 2007, we and, for limited purposes, Alnylam Europe AG, or Alnylam Europe, entered into a license and collaboration agreement with Roche. Under the license and collaboration agreement, which became effective in August 2007, 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. The license is initially limited to the therapeutic areas of oncology, respiratory diseases, metabolic diseases and certain liver diseases, and may be expanded to include up to 18 additional therapeutic areas, comprising substantially all other fields of human disease, as identified and agreed upon by the parties, upon payment to us by Roche of an additional \$50.0 million for each additional therapeutic area, if any.

In consideration for the rights granted to Roche under the license and collaboration agreement, Roche paid us \$273.5 million in upfront cash payments. In addition, in exchange for our contributions under the collaboration agreement, for each RNAi therapeutic product developed by Roche, its affiliates or sublicensees under the collaboration agreement, we are entitled to receive milestone payments upon achievement of specified development and sales events, totaling up to an aggregate of \$100.0 million per therapeutic target, together with royalty payments based on worldwide annual net sales, if any. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any milestone or royalty payments from Roche.

Under the license and collaboration agreement, we and Roche also agreed to collaborate on the discovery of RNAi therapeutic products directed to one or more disease targets, subject to our contractual obligations to third parties. In October 2009, we and Roche advanced our alliance to initiate this therapeutic collaboration stage, referred to as the Discovery Collaboration. Under the Discovery Collaboration, we and Roche are collaborating on the discovery and development of specific RNAi therapeutic products and each party contributes key delivery technologies in the effort, which is focused on specific disease targets. We and Roche intend to co-develop and co-commercialize RNAi therapeutic products in the U.S. market and we are eligible to receive additional milestone and royalty payments for products developed in the rest of the world, if any. After a pre-specified period of collaborative activities, each party will have the option to opt-out of the day-to-day development activities in exchange for reduced milestones and royalty payments in the future. The Discovery Collaboration is governed by the joint steering committee that is comprised of an equal number of representatives from each party.

In connection with the execution of the license and collaboration agreement, we executed a common stock purchase agreement with Roche Finance Ltd, or Roche Finance, an affiliate of Roche. Under the terms of the common stock

purchase agreement, in August 2007, Roche Finance purchased 1,975,000 shares of our common stock at \$21.50 per share, for an aggregate purchase price of \$42.5 million.

In connection with the execution of the license and collaboration agreement and the common stock purchase agreement, we also executed a stock purchase agreement with Alnylam Europe and Roche Beteiligungs GmbH, or Roche Germany, an affiliate of Roche. Under the terms of the Alnylam Europe stock purchase agreement, we created a new, wholly-owned German limited liability company, Roche Kulmbach, into which substantially all of

**Table of Contents**

the non-intellectual property assets of Alnylam Europe were transferred, and Roche Germany purchased from us all of the issued and outstanding shares of Roche Kulmbach for an aggregate purchase price of \$15.0 million. The Alnylam Europe stock purchase agreement included transition services that were performed by Roche Kulmbach employees at various levels through August 2008. We reimbursed Roche for these services at an agreed-upon rate.

In connection with the license and collaboration agreement and the common stock purchase agreement, during 2007, we paid \$27.5 million in license fees to our licensors, primarily Isis, in accordance with the applicable license agreements with those parties. These fees were charged to research and development expense.

**Takeda.** 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 an upfront payment of \$100.0 million. Takeda is also required to make the 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 due upon achievement of specified technology transfer activities, but no later than May 2010, and \$10.0 million of which is due upon the achievement of specified technology transfer activities within 24 to 36 months after 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, if any, comprising substantially all other fields of human disease, as identified and agreed upon by the parties. In addition, for each RNAi therapeutic product developed by Takeda, its affiliates and sublicensees, we are entitled to receive specified development and commercialization milestones, totaling up to \$171.0 million per product, together with royalty payments based on worldwide annual net sales, if any. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any milestone or royalty payments from Takeda.

Pursuant to the Takeda agreement, we and Takeda are also collaborating 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 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-RSV 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.

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

**Discovery and Development Alliances.**

**Isis.** In April 2009, we and Isis amended and restated our existing strategic collaboration and license agreement, originally entered into in March 2004, to extend the broad cross-licensing arrangement regarding double-stranded RNAi that was established in 2004, pursuant to which Isis granted us licenses to its current and

**Table of Contents**

future patents and patent applications relating to chemistry and to RNA-targeting mechanisms for the research, development and commercialization of double-stranded RNA, or dsRNA products. We have the right to use Isis technologies in our development programs or in collaborations, and Isis has agreed not to grant licenses under these patents to any other organization for the discovery, development or commercialization of dsRNA products designed to work through an RNAi mechanism, except in the context of a collaboration in which Isis plays an active role. We granted Isis non-exclusive licenses to our current and future patents and patent applications relating to RNA-targeting mechanisms and to chemistry for research use. We also granted Isis the non-exclusive right to develop and commercialize dsRNA products developed using RNAi technology against a limited number of targets. In addition, we granted Isis non-exclusive rights to research, develop and commercialize single-stranded RNA products.

We agreed to pay Isis milestone payments, totaling up to approximately \$3.4 million, upon the occurrence of specified development and regulatory events, and royalties on sales, if any, for each product that we or a collaborator develops using Isis intellectual property. In addition, we agreed to pay to Isis a percentage of specified fees from strategic collaborations we may enter into that include access to the Isis intellectual property.

Isis agreed to pay us, per therapeutic target, a license fee of \$0.5 million, and milestone payments totaling approximately \$3.4 million, payable upon the occurrence of specified development and regulatory events, and royalties on sales, if any, for each product developed by Isis or a collaborator that utilizes our intellectual property. Isis has the right to elect up to ten non-exclusive target licenses under the agreement and has the right to purchase one additional non-exclusive target per year during the term of the collaboration.

As part of the amended and restated Isis agreement, we and Isis established a new collaborative effort focused on the development of ssRNAi technology. Under the amended and restated Isis agreement, we obtained from Isis a co-exclusive, worldwide license to Isis' current and future patents and patent applications relating to chemistry and RNA-targeting mechanisms to research, develop and commercialize ssRNAi products. Each party has the opportunity to discover and develop drugs employing the ssRNAi technology. Under the terms of the amended and restated Isis agreement, we will potentially pay Isis up to an aggregate of \$31.0 million in license fees, payable in four tranches, that include \$11.0 million paid on signing, \$10.0 million payable in October 2010, or if and when *in vivo* efficacy in rodents is demonstrated if sooner, \$5.0 million upon achievement of *in vivo* efficacy in non-human primates, and \$5.0 million upon initiation of the first clinical trial with an ssRNAi drug, subject to our right to unilaterally terminate the research program. We are funding research activities at a minimum of \$3.0 million each year for three years with research and development activities conducted by both us and Isis. If we develop and commercialize drugs utilizing ssRNAi technology on our own or with a partner, we would be required to make milestone payments to Isis, totaling up to \$18.5 million per product, as well as royalties. Also, Isis initially is eligible to receive up to 50% of any sublicense payments due to us from a third party based on our partnering of ssRNAi products, which amount will decline over time as our investment in the technology and drugs increases. In turn, we are eligible to receive up to five percent of any sublicense payments due to Isis from a third party based on Isis' partnering of ssRNAi products.

We have the unilateral right to terminate the ssRNAi research program before September 30, 2010, in which event any licenses to ssRNAi products granted by Isis to us under the amended and restated Isis agreement, and any obligation thereunder by us to pay milestone payments, royalties or sublicense payments to Isis for such ssRNAi products, would also terminate.

**Novartis.** Beginning in September 2005, we entered into a series of transactions with Novartis which we refer to as our broad Novartis alliance. At that time, we and Novartis executed a stock purchase agreement and an investor rights agreement. When the transactions contemplated by the stock purchase agreement closed in October 2005, the investor rights agreement became effective and we and Novartis executed a research collaboration and license agreement. The collaboration and license agreement had an initial term of three years, with an option for two additional one-year extensions at the election of Novartis. In July 2009, Novartis elected to further extend the term for the fifth and final

planned year, through October 2010.

Under the terms of the collaboration and license agreement, we and Novartis 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. In consideration for rights granted to Novartis under the collaboration and license agreement, Novartis made an upfront payment of \$10.0 million to us in October 2005, partly to reimburse prior



**Table of Contents**

costs incurred by us to develop *in vivo* RNAi technology. The collaboration and license agreement also includes terms under which Novartis has been providing us with research funding and development milestone payments, and may provide us in the future with sales milestone payments as well as royalties on annual net sales of products resulting from the collaboration, if any. The amount of research funding provided by Novartis under the collaboration and license agreement during the research term is dependent upon the number of active programs on which we are collaborating with them at any given time and the number of our employees that are working on those programs, in respect of which Novartis reimburses us at an agreed upon rate. Under the terms of the collaboration and license agreement, Novartis has the right to select up to 30 exclusive targets to include in the collaboration, which number may be increased to 40 under certain circumstances and upon additional payments. For RNAi therapeutic products developed under the agreement, if any, we would be entitled to receive milestone payments upon achievement of certain specified development and annual net sales events, up to an aggregate of \$75.0 million per therapeutic product. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive additional milestone payments or any royalty payments from Novartis.

The collaboration and license agreement also provides Novartis with a non-exclusive option to integrate into its operations our intellectual property relating to RNAi technology, excluding any technology related to delivery of nucleic acid based molecules. Novartis may exercise this integration option at any point during the research term, which term is currently expected to expire in the fourth quarter of 2010. In connection with the exercise of the integration option, Novartis would be required to make additional payments to us totaling \$100.0 million, payable in full at the time of exercise, which payments would include an option exercise fee, a milestone based on the overall success of the collaboration and pre-paid milestones and royalties that could become due as a result of future development of products using our technology. This amount would be offset by any license fees due to our licensors in accordance with the applicable license agreements with those parties. In addition, under this license grant, Novartis may be required to make milestone and royalty payments to us in connection with the development and commercialization of RNAi therapeutic products, if any. The license grant under the integration option, if exercised by Novartis, would be structured similarly to our non-exclusive platform licenses with Roche and Takeda.

Under the terms of the stock purchase agreement, in October 2005, Novartis purchased 5,267,865 shares of our 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 our outstanding common stock as of the date of issuance. In addition, under the investor rights agreement, we granted Novartis rights to acquire additional equity securities in the event that we propose to sell or issue any equity securities, subject to specified exceptions, as described in the investor rights agreement, such that Novartis would be able to maintain its then-current ownership percentage in our outstanding common stock. Pursuant to terms of the investor rights agreement, in May 2008, Novartis purchased 213,888 shares of our common stock at a purchase price of \$25.29 per share resulting in a payment to us of \$5.4 million. In May 2009, Novartis purchased 65,922 shares of our common stock at a purchase price of \$17.50 per share, resulting in an aggregate payment to us of \$1.2 million. This purchase allowed Novartis to maintain its ownership position of 13.4% of our outstanding common stock. The exercises of this right did not result in any changes to existing rights or any additional rights to Novartis. Further, during the term described in the investor rights agreement, Novartis is permitted to own no more than 19.9% of our outstanding shares. At December 31, 2009, Novartis owned 13.3% of our outstanding common stock.

In addition to the broad Novartis alliance, in February 2006, we entered into the Novartis flu alliance. Under the terms of the Novartis flu alliance, we and Novartis had joint responsibility for the development of RNAi therapeutics for pandemic flu. This program was stopped during 2008 and currently there are no specific resource commitments for this program.

**Biogen Idec.** In September 2006, we entered into a collaboration and license agreement with Biogen Idec. The collaboration is focused on the discovery and development of therapeutics based on RNAi for the potential treatment

of PML. Under the terms of the Biogen Idec agreement, we granted Biogen Idec an exclusive license to distribute, market and sell certain RNAi therapeutics to treat PML and Biogen Idec has agreed to fund all related research and development activities. We received an upfront \$5.0 million payment from Biogen Idec. In addition, upon the successful development and utilization of a product resulting from the collaboration, if any, Biogen Idec would be required to pay us milestone payments, totaling \$51.0 million, and royalty payments on sales, if any. Due

**Table of Contents**

to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any milestone or royalty payments from Biogen Idec. The pace and scope of future development of this program is the responsibility of Biogen Idec. We expect to expend limited resources on this program in 2010.

**Product Alliances.**

**Medtronic.** In July 2007, we entered into an amended and restated collaboration agreement with Medtronic to pursue the development of therapeutic products for the treatment of neurodegenerative disorders. The amended and restated collaboration agreement supersedes the collaboration agreement entered into by the parties in February 2005, and continues the existing collaboration between the parties focusing on the delivery of RNAi therapeutics to specific areas of the brain using implantable infusion systems.

Under the terms of the amended and restated collaboration agreement, we and Medtronic are continuing our existing development program focused on developing a combination drug-device product for the treatment of Huntington's disease. In addition, we and Medtronic may jointly agree to collaborate on additional product development programs for the treatment of other neurodegenerative diseases, which can be addressed by the delivery of siRNAs discovered and developed using our RNAi therapeutics platform to the human nervous system through implantable infusion devices developed by Medtronic. We are responsible for supplying the siRNA component and Medtronic is responsible for supplying the device component of any product resulting from the collaboration.

With respect to the initial product development program focused on Huntington's disease, each party is funding 50% of the development efforts for the United States while Medtronic is responsible for funding development efforts outside the United States. Medtronic will commercialize any resulting products and pay royalties to us based on net sales of such products, if any, which royalties in the United States are designed to approximate 50% of the profit associated with the sale of such product and which royalties in Europe are similar to more traditional pharmaceutical royalties, in that they are intended to reflect each party's contribution.

Each party has the right to opt-out of its obligation to fund the program under the agreement at certain stages, and the agreement provides for revised economics based on the timing of any such opt-out. Other than pursuant to the initial product development program, and subject to specified exceptions, neither party may research, develop, manufacture or commercialize products that use implanted infusion devices for the direct delivery of siRNAs to the human nervous system to treat Huntington's disease during the term of such program.

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

Under the terms of the Kyowa Hakko Kirin agreement, in June 2008, Kyowa Hakko Kirin paid us an upfront cash payment of \$15.0 million. In addition, Kyowa Hakko Kirin is required to make payments to us upon achievement of specified development and sales milestones totaling up to \$78.0 million, and royalty payments based on annual net sales, if any, of RNAi therapeutics for RSV by Kyowa Hakko Kirin, its affiliates and sublicensees in the licensed territory. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any milestone or royalty payments from Kyowa Hakko Kirin.

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

**Table of Contents**

territory. We are responsible for supply of the product to Kyowa Hakko Kirin under a supply agreement unless Kyowa Hakko Kirin 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.

**Cubist.** In January 2009, we entered into a license and collaboration agreement with Cubist to develop and commercialize therapeutic products based on certain of our RNAi technology for the treatment of RSV. Licensed products initially included ALN-RSV01, as well as several other second-generation RNAi-based RSV inhibitors. In November 2009, we and Cubist entered into an amendment to our license and collaboration agreement, which provides that we and Cubist will focus our collaboration and joint development efforts on ALN-RSV02, a second-generation compound, intended for use in pediatric patients. Consistent with the original license and collaboration agreement, we and Cubist each bears one-half of the related development costs for ALN-RSV02. Pursuant to the terms of the amendment, we are also continuing to develop ALN-RSV01 for adult transplant patients at our sole discretion and expense. Cubist has the right to resume the collaboration on ALN-RSV01 in the future, which right may be exercised for a specified period of time following the completion of our Phase IIb trial of ALN-RSV01 in adult lung transplant patients infected with RSV, subject to the payment by Cubist of an opt-in fee representing reimbursement of an agreed upon percentage of certain of our development expenses for ALN-RSV01.

Under the terms of the Cubist agreement, we and Cubist share responsibility for developing licensed products in North America and each bears one-half of the related development costs, subject to the terms of the November 2009 amendment. Our collaboration with Cubist for the development of licensed products in North America is governed by a joint steering committee comprised of an equal number of representatives from each party. Cubist will have the sole right to commercialize licensed products in North America with costs associated with such activities and any resulting profits or losses to be split equally between us and Cubist. Throughout the rest of the world, referred to as the Royalty Territory, excluding Asia, where we have previously partnered our ALN-RSV program with Kyowa Hakko Kirin, Cubist has an exclusive, royalty-bearing license to develop and commercialize licensed products.

In consideration for the rights granted to Cubist under the agreement, in January 2009, Cubist paid us an upfront cash payment of \$20.0 million. Cubist also has an obligation under the agreement to pay us milestone payments, totaling up to an aggregate of \$82.5 million, upon the achievement of specified development and sales events in the Royalty Territory. In addition, if licensed products are successfully developed, Cubist will be required to pay us double digit royalties on net sales of licensed products in the Royalty Territory, if any, subject to offsets under certain circumstances. Upon achievement of certain development milestones, we will have the right to convert the North American co-development and profit sharing arrangement into a royalty-bearing license and, in addition to royalties on net sales in North America, will be entitled to receive additional milestone payments totaling up to an aggregate of \$130.0 million upon achievement of specified development and sales events in North America, subject to the timing of the conversion by us and the regulatory status of a licensed product at the time of conversion. If we make the conversion to a royalty-bearing license with respect to North America, then North America becomes part of the Royalty Territory. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any milestone or royalty payments from Cubist.

In connection with the Cubist agreement, during 2009, we paid \$1.0 million of license fees to our licensors, primarily Isis, in accordance with the applicable license agreements with those parties. These fees were charged to research and development expense.

***Delivery Initiatives***

We are working internally and with third-party collaborators to extend our capabilities in developing technology to achieve effective and safe delivery of RNAi therapeutics to a broad spectrum of organ and tissue types. In connection with these efforts, we have entered into a number of agreements to evaluate and gain access to certain delivery

technologies. In some instances, we are also providing funding to support the advancement of these delivery technologies. We believe that we have made considerable progress in developing our product platform. Over the past 12 to 18 months, we have made several of what we believe to be major advances relating to the delivery of RNAi therapeutics, both internally and together with our collaborators. The first relates to the discovery of new LNP compositions that provide dramatic improvements in the potency of gene silencing as compared to first generation

**Table of Contents**

LNPs. Additionally, we believe we have discovered an important *in vivo* mechanism for delivery relating to the role of endogenous apolipoprotein E, or ApoE, a plasma protein involved in lipoprotein metabolism, in the delivery of certain LNPs into the cytoplasm of certain cells. The latter discovery has allowed the specific targeting of LNPs and allows the possibility of delivery beyond the liver. We discuss these advances and our overall delivery efforts in more detail in the section entitled "Delivery Initiatives" found in Part I, Item 1 of this annual report on Form 10-K.

In May 2007, we entered into an agreement with the David H. Koch Institute for Integrative Cancer Research at MIT, 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 for the discovery, development and commercialization of LNP formulations for the delivery of RNAi therapeutics and a non-exclusive worldwide license to certain liposomal delivery formulation technology of Protiva Biotherapeutics Inc., or Protiva, for the discovery, development and commercialization of certain LNP formulations for the delivery of RNAi therapeutics. In May 2008, Tekmira acquired 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 these agreements, 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 for RNAi, which we believe are critical for the use of LNP delivery technology. In July 2009, we and Tekmira agreed to jointly participate in a new research collaboration with scientists at UBC and AICana focused on the discovery of novel lipids for use in LNPs for the systemic delivery of RNAi therapeutics. We are funding the collaborative research over a two-year period, and the work is being conducted by our scientists together with scientists at UBC and AICana. We will receive exclusive rights to all new inventions as well as sole rights to sublicense any resulting intellectual property to our current and future collaborators. Tekmira will receive rights to use new inventions for their own RNAi therapeutic programs that are licensed under our InterfeRx program.

We are developing ALN-VSP, a systemically delivered RNAi therapeutic candidate, for the treatment of primary and secondary liver cancer. ALN-VSP contains two siRNAs formulated using the first generation LNP formulation known as stable nucleic acid-lipid particles, or SNALP, developed in collaboration with Tekmira. We also have rights to use SNALP technology in the advancement of our other systemically delivered RNAi therapeutic programs, and are advancing ALN-TTR01, for the treatment of ATTR, utilizing a first generation SNALP formulation. In parallel with ALN-TTR01, we are advancing ALN-TTR02 utilizing second-generation LNPs. In addition, we have published pre-clinical results from development programs for other systemically delivered RNAi therapeutic candidates, including ALN-PCS, for the treatment of hypercholesterolemia, which we recently identified as our next clinical candidate. ALN-PCS is being advanced using second-generation LNPs for systemic delivery.

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 year ended December 31, 2008. During 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 are pursuing additional approaches for delivery that include other LNP formulations, mimetic lipoprotein particles, or MLPs, siRNA conjugation strategies and ssRNAi, among others. In addition, we have other RNAi therapeutic delivery collaborations and intend to continue to collaborate with government, academic and corporate third parties to evaluate and gain access to different delivery technologies.

***Government Funding***

**NIH.** In September 2006, the NIAID, a component of NIH, 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. As a result of the continued progress of this program, the NIAID has appropriated the entire \$23.0 million over the four-year term of the contract, which will be completed in September 2010.



## **Table of Contents**

**Department of Defense.** In August 2007, DTRA awarded us a contract to advance the development of a broad spectrum RNAi anti-viral therapeutic for hemorrhagic fever virus. The government initially committed to pay us up to \$10.9 million through February 2009, which included a six-month extension granted by DTRA in July 2008. Following a program review in early 2009, we and DTRA determined not to continue this program and accordingly, the remaining funds of up to \$27.7 million were not accessed.

### ***microRNAi-based Therapeutics***

**Regulus.** In September 2007, we and Isis established Regulus, a company focused on the discovery, development and commercialization of microRNA-based therapeutics. Regulus combines our and Isis technologies, know-how and intellectual property relating to microRNA-based therapeutics. Since microRNAs are believed to regulate the expression of broad networks of genes and biological pathways, microRNA-based therapeutics define a new and potentially high-impact strategy to target multiple points on disease pathways.

Regulus, which initially was established as a limited liability company, converted to a C corporation as of January 2, 2009 and changed its name to Regulus Therapeutics Inc. In consideration for our and Isis initial interests in Regulus, we and Isis each granted Regulus exclusive licenses to our intellectual property for certain microRNA-based therapeutics as well as certain patents in the microRNA field. In addition, we made an initial cash contribution to Regulus of \$10.0 million, resulting in us and Isis making initial capital contributions to Regulus of approximately equal aggregate value. In addition, in March 2009, we and Isis each purchased \$10.0 million of Series A preferred stock of Regulus. We and Isis currently own approximately 49% and 51%, respectively, of Regulus and there are currently no other third party investors in Regulus. Regulus continues to operate as an independent company with a separate board of directors, scientific advisory board and management team, some of whom have options to purchase common stock of Regulus. Members of the board of directors of Regulus who are our employees or Isis employees are not eligible to receive options to purchase Regulus common stock.

Regulus most advanced program, which is in pre-clinical research, is a microRNA-based therapeutic candidate that targets miR-122. miR-122 is a liver-expressed microRNA that has been shown to be a critical endogenous host factor for the replication of HCV, and anti-miRs targeting miR-122 have been shown to block HCV infection. HCV infection is a significant disease worldwide, for which emerging therapies target viral genes and, therefore, are prone to viral resistance. Regulus is also pursuing a program that targets miR-21. Pre-clinical studies by Regulus and collaborators have shown that miR-21 is implicated in several therapeutic areas, including heart failure and fibrosis. In addition to these programs, Regulus is also actively exploring additional areas for development of microRNA-based therapeutics, including cancer, other viral diseases, metabolic disorders and inflammatory diseases.

In April 2008, Regulus 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 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 us and Isis) that will convert into Regulus common stock under certain specified circumstances. Regulus 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, if any. In May 2009, Regulus achieved the first demonstration of a pharmacological effect in immune cells by specific microRNA inhibition, the initial discovery milestone under the GSK alliance, which triggered a payment under the agreement.

In February 2010, Regulus and GSK established a new collaboration to develop and commercialize microRNA-based therapeutics targeting miR-122 in all fields, with HCV infection as the lead indication. This new collaboration includes the potential for Regulus to earn more than \$150.0 million in upfront and milestone payments, in addition to

royalties, on worldwide sales of products, if any, as Regulus and GSK advance microRNA-based therapeutics targeting miR-122.

**Table of Contents**

***Alnylam Biotherapeutics***

During 2009, we presented new data regarding the application of RNAi technology to improve the manufacturing processes for biologics, which is comprised of recombinant proteins, monoclonal antibodies, and vaccines. This initiative, which we are advancing in an internal effort referred to as Alnylam Biotherapeutics, has the potential to create new business opportunities. In particular, we are advancing RNAi technologies to improve the quantity and quality of biologics manufacturing processes using mammalian cell culture, such as Chinese hamster ovary cells, or CHO cells. This RNAi technology potentially could be applied to the improvement of manufacturing processes for existing marketed drugs, new drugs in development and for the emerging biosimilars market. We have developed proprietary delivery lipids that enable the efficient transfection of siRNAs into CHO cells when grown in suspension culture. As Alnylam Biotherapeutics advances the technology, it plans to seek partnerships with established biologic manufacturers, selling licenses, products and services.

**Critical Accounting Policies and Estimates**

Our discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States of America, or GAAP. The preparation of our consolidated financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, revenues and expenses and disclosure of contingent liabilities in our consolidated financial statements. Actual results may differ from these estimates under different assumptions or conditions and could have a material impact on our reported results. While our significant accounting policies are more fully described in the Notes to our consolidated financial statements included elsewhere in this annual report on Form 10-K, we believe the following accounting policies to be the most critical in understanding the judgments and estimates we use in preparing our consolidated financial statements:

***Revenue Recognition***

Our business strategy includes entering into collaborative license and development agreements with biotechnology and pharmaceutical companies for the development and commercialization of our product candidates. The terms of the agreements typically include non-refundable license fees, funding of research and development, payments based upon achievement of clinical and pre-clinical development milestones, manufacturing services and royalties on product sales.

Non-refundable license fees are recognized as revenue upon delivery of the license only if we have a contractual right to receive such payment, the contract price is fixed or determinable, the collection of the resulting receivable is reasonably assured and we have no further performance obligations under the license agreement. Multiple element arrangements, such as license and development arrangements, are analyzed to determine whether the deliverables, which often include a license and performance obligations such as research and steering committee services, can be separated or whether they must be accounted for as a single unit of accounting. We recognize upfront license payments as revenue upon delivery of the license only if the license has stand-alone value and the fair value of the undelivered performance obligations, typically including research and/or steering committee services, can be determined. If the fair value of the undelivered performance obligations can be determined, such obligations would then be accounted for separately as performed. If the license is considered to either not have stand-alone value or have stand-alone value but the fair value of any of the undelivered performance obligations cannot be determined, the arrangement would then be accounted for as a single unit of accounting and the license payments and payments for performance obligations are recognized as revenue over the estimated period of when the performance obligations are performed.

Whenever we determine that an arrangement should be accounted for as a single unit of accounting, we must determine the period over which the performance obligations will be performed and revenue will be recognized. Revenue will be recognized using either a proportional performance or straight-line method. We recognize revenue using the proportional performance method when we can reasonably estimate the level of effort required to complete our performance obligations under an arrangement and such performance obligations are provided on a best-efforts basis. Direct labor hours or full-time equivalents are typically used as the measure of performance.

**Table of Contents**

Revenue recognized under the proportional performance method would be determined by multiplying the total payments under the contract, excluding royalties and payments contingent upon achievement of substantive milestones, by the ratio of level of effort incurred to date to estimated total level of effort required to complete our performance obligations under the arrangement. Revenue is limited to the lesser of the cumulative amount of payments received or the cumulative amount of revenue earned, as determined using the proportional performance method, as of the period ending date.

If we cannot reasonably estimate the level of effort required to complete our performance obligations under an arrangement, then revenue under the arrangement will be recognized as revenue on a straight-line basis over the period we expect to complete our performance obligations. Revenue is limited to the lesser of the cumulative amount of payments received or the cumulative amount of revenue earned, as determined using the straight-line method, as of the period ending date.

Significant management judgment is required in determining the level of effort required under an arrangement and the period over which we are expected to complete our performance obligations under an arrangement. Steering committee services that are not inconsequential or perfunctory and that are determined to be performance obligations are combined with other research services or performance obligations required under an arrangement, if any, in determining the level of effort required in an arrangement and the period over which we expect to complete our aggregate performance obligations.

Many of our collaboration agreements entitle us to additional payments upon the achievement of performance-based milestones. If the achievement of a milestone is considered probable at the inception of the collaboration, the related milestone payment is included with other collaboration consideration, such as upfront fees and research funding, in our revenue model. Milestones that involve substantial effort on our part and the achievement of which are not considered probable at the inception of the collaboration are considered substantive milestones. Substantive milestones are included in our revenue model when achievement of the milestone is considered probable. As future substantive milestones are achieved, a portion of the milestone payment, equal to the percentage of the performance period completed when the milestone is achieved, multiplied by the amount of the milestone payment, will be recognized as revenue upon achievement of such milestone. The remaining portion of the milestone will be recognized over the remaining performance period using the proportional performance or straight-line method. Milestones that are tied to regulatory approval are not considered probable of being achieved until such approval is received. Milestones tied to counter-party performance are not included in our revenue model until the performance conditions are met.

Steering committee services that are not inconsequential or perfunctory and that are determined to be performance obligations are combined with other research services or performance obligations required under an arrangement, if any, in determining the level of effort required in an arrangement and the period over which we expect to complete our aggregate performance obligations.

For revenue generating arrangements where we, as a vendor, provide consideration to a licensor or collaborator, as a customer, we apply the accounting standard that governs such transactions. This standard addresses the accounting for revenue arrangements where both the vendor and the customer make cash payments to each other for services and/or products. A payment to a customer is presumed to be a reduction of the selling price unless we receive an identifiable benefit for the payment and we can reasonably estimate the fair value of the benefit received. Payments to a customer that are deemed a reduction of selling price are recorded first as a reduction of revenue, to the extent of both cumulative revenue recorded to date and probable future revenues, which include any unamortized deferred revenue balances, under all arrangements with such customer, and then as an expense. Payments that are not deemed to be a reduction of selling price would be recorded as an expense.

We evaluate our collaborative agreements for proper classification in our consolidated statements of operations based on the nature of the underlying activity. Transactions between collaborators recorded in our consolidated statements of operations are recorded on either a gross or net basis, depending on the characteristics of the collaborative relationship. We generally reflect amounts due under our collaborative agreements related to cost-sharing of development activities as a reduction of research and development expense.

## Table of Contents

Amounts received prior to satisfying the above revenue recognition criteria are recorded as deferred revenue in the accompanying consolidated balance sheets. Amounts not expected to be recognized within the next 12 months are classified as long-term deferred revenue.

Although we follow detailed guidelines in measuring revenue, certain judgments affect the application of our revenue policy. For example, in connection with our existing collaboration agreements, we have recorded on our balance sheet short-term and long-term deferred revenue based on our best estimate of when such revenue will be recognized. Short-term deferred revenue consists of amounts that are expected to be recognized as revenue in the next 12 months. Amounts that we expect will not be recognized prior to the next 12 months are classified as long-term deferred revenue. However, this estimate is based on our current operating plan and, if our operating plan should change in the future, we may recognize a different amount of deferred revenue over the next 12-month period.

The estimate of deferred revenue also reflects management's estimate of the periods of our involvement in certain of our collaborations. Our performance obligations under these collaborations consist of participation on steering committees and the performance of other research and development services. In certain instances, the timing of satisfying these obligations can be difficult to estimate. Accordingly, our estimates may change in the future. Such changes to estimates would result in a change in revenue recognition amounts. If these estimates and judgments change over the course of these agreements, it may affect the timing and amount of revenue that we recognize and record in future periods.

As of December 31, 2009, we had short-term and long-term deferred revenue of \$81.9 million and \$189.9 million, respectively, related to our collaborations.

**Novartis.** In consideration for rights granted to Novartis under the collaboration and license agreement, Novartis made an upfront payment of \$10.0 million to us in October 2005 to partly reimburse costs previously incurred by us to develop *in vivo* RNAi technology. The collaboration and license agreement includes terms under which Novartis is providing us with research funding. In addition, for RNAi therapeutic products developed under the agreement, if any, we are entitled to receive milestone payments upon achievement of certain specified development and annual net sales events, up to an aggregate of \$75.0 million per therapeutic product. We initially recorded as deferred revenue the non-refundable \$10.0 million upfront payment and the \$6.4 million premium that represented the difference between the purchase price and the closing price of our common stock on the date of the stock purchase from Novartis. In addition to these payments, research funding and certain milestone payments, the receipt of which is considered probable, are being amortized into revenue using the proportional performance method over the estimated duration of the collaboration and license agreement, or ten years. Under this method, we estimate the level of effort to be expended over the term of the agreement and recognize revenue based on the lesser of the amount calculated based on the proportional performance of total expected revenue or the amount of non-refundable payments earned.

As future substantive milestones are achieved, and to the extent they are within the period of performance, milestone payments will be recognized as revenue on a proportional performance basis over the contract's entire performance period, starting with the contract's commencement. A portion of the milestone payment, equal to the percentage of total performance completed when the milestone is achieved, multiplied by the milestone payment, will be recognized as revenue upon achievement of the milestone. The remaining portion of the milestone will be recognized over the remaining performance period under the proportional performance method.

We believe our estimated period of performance under the Novartis collaboration and license agreement is ten years, which includes the three-year initial term of the agreement, the two one-year extensions elected by Novartis and limited support as part of a technology transfer until 2015, the fifth anniversary of the termination of the collaboration and license agreement. We continue to use an expected term of ten years in our proportional performance model. We reevaluate the expected term when new information is known that could affect our estimate. In the event our period of

performance is different than we estimated, revenue recognition will be adjusted on a prospective basis.

**Roche.** We received aggregate proceeds from Roche of \$331.0 million in August 2007. We initially recorded \$278.2 million of these proceeds as deferred revenue in connection with this alliance. We allocated \$51.3 million



**Table of Contents**

and \$1.5 million for financial statement purposes related to the common stock issuance and the net book value of Alnylam Europe, respectively. In exchange for our contributions under the collaboration agreement, for each RNAi therapeutic product developed by Roche, its affiliates or sublicensees under the collaboration agreement, we are entitled to receive milestone payments upon achievement of specified development and sales events, totaling up to an aggregate of \$100.0 million per therapeutic target, together with royalty payments based on worldwide annual net sales, if any. In addition, we agreed with Roche to collaborate on the discovery of RNAi therapeutic products directed to one or more disease targets, subject to our existing contractual obligations to third parties. In October 2009, we and Roche advanced our alliance to initiate this therapeutic collaboration stage. Under this Discovery Collaboration, we and Roche are collaborating on the discovery and development of specific RNAi therapeutic products and each party contributes key delivery technologies in the effort, which is focused on specific disease targets. The Discovery Collaboration is governed by the joint steering committee that is comprised of an equal number of representatives from each party.

We have 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 we are performing under the Discovery Collaboration. We have determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, 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, we base our 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 license and collaboration agreement. We are recognizing the Roche-related revenue on a straight-line basis over five years because we cannot reasonably estimate the total level of effort required to complete our service obligations under the license and collaboration agreement in order to utilize a proportional performance model. As future substantive milestones are achieved, a portion of the milestone payment, equal to the percentage of the performance period completed when the milestone is achieved, multiplied by the amount of the milestone payment, will be recognized as revenue upon achievement of such milestone. The remaining portion of the milestone will be recognized over the remaining performance period on a straight-line basis.

**Takeda.** 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 June 2008, Takeda paid us an upfront payment of \$100.0 million. 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 paid in October 2008, \$20.0 million of which is due upon achievement of specified technology transfer activities, but no later than May 2010, and \$10.0 million of which is due upon achievement of specified technology transfer activities within 24 to 36 months after 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, if any, comprising substantially all other fields of human disease, as identified and agreed upon by the parties. In addition, for each RNAi therapeutic product developed by Takeda, its affiliates and sublicensees, we are entitled to receive specified development and commercialization milestones, totaling up to \$171.0 million per product, together with royalty payments based on worldwide annual net sales, if any.

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 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-RSV 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 JTTC, a JRCC and a JDCC, each of which is comprised of an equal number of representatives from each party.

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

**Table of Contents**

under the research collaboration with Takeda. We have determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, 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. Under the Takeda agreement, the last elements to be delivered are the JDCC and JTTC services, each of which has a 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 \$30.0 million of remaining technology transfer milestones, the receipt of which we believe is probable, 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, in order to utilize a proportional performance model. As future substantive milestones are achieved, a portion of the milestone payment, equal to the percentage of the performance period completed when the milestone is achieved, multiplied by the amount of the milestone payment, will be recognized as revenue upon achievement of such milestone. The remaining portion of the milestone will be recognized over the remaining performance period on a straight-line basis.

**Kyowa Hakko Kirin.** Under the terms of the Kyowa Hakko Kirin agreement, in June 2008, Kyowa Hakko Kirin paid us an upfront cash payment of \$15.0 million. In addition, Kyowa Hakko Kirin is required to make payments to us upon achievement of specified development and sales milestones totaling up to \$78.0 million, and royalty payments based on annual net sales, if any, of RNAi therapeutics for RSV by Kyowa Hakko Kirin, its affiliates and sublicenses in the licensed territory.

Our collaboration with Kyowa Hakko Kirin is governed by a joint steering committee that is comprised of an equal number of representatives from each party. Kyowa Hakko Kirin is responsible, at its expense, for all development activities under the development plan that are reasonably necessary for the regulatory approval and commercialization of an RNAi therapeutic for the treatment of RSV in Japan and the rest of the licensed territory. We are responsible for supply of the product to Kyowa Hakko Kirin under a supply agreement unless Kyowa Hakko Kirin 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.

We have determined that the deliverables under the Kyowa Hakko Kirin 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 the accounting guidance governing revenue recognition on multiple element arrangements, the individual deliverables are not separable and, accordingly, must be accounted for as a single unit of accounting. We are currently unable to reasonably estimate our period of performance under the Kyowa Hakko Kirin agreement, as we are unable to estimate the timeline of our deliverables related to the fixed-price option granted to Kyowa Hakko Kirin for any additional compounds. We are deferring all revenue under the Kyowa Hakko Kirin 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 Kirin agreement.

**Cubist.** Under the terms of the Cubist agreement, we and Cubist share responsibility for developing licensed products in North America and each bears one-half of the related development costs, subject to the terms of the November 2009 amendment. Our collaboration with Cubist for the development of licensed products in North America is governed by a joint steering committee comprised of an equal number of representatives from each party. Cubist will have the sole right to commercialize licensed products in North America with costs associated with such activities and any resulting profits or losses to be split equally between us and Cubist. Throughout the rest of the world, referred to as the Royalty Territory, excluding Asia, where we have previously partnered our ALN-RSV program with Kyowa Hakko Kirin, Cubist has an exclusive, royalty-bearing license to develop and commercialize licensed products.

In consideration for the rights granted to Cubist under the agreement, in January 2009, Cubist paid us an upfront cash payment of \$20.0 million. Cubist also has an obligation under the agreement to pay us milestone payments, totaling up to an aggregate of \$82.5 million, upon the achievement of specified development and sales events in the Royalty Territory. In addition, if licensed products are successfully developed, Cubist will be required to pay us double digit royalties on net sales of licensed products in the Royalty Territory, if any, subject to offsets under certain circumstances. Upon achievement of certain development milestones, we will have the right to

**Table of Contents**

convert the North American co-development and profit sharing arrangement into a royalty-bearing license and, in addition to royalties on net sales in North America, will be entitled to receive additional milestone payments totaling up to an aggregate of \$130.0 million upon achievement of specified development and sales events in North America, subject to the timing of the conversion by us and the regulatory status of a licensed product at the time of conversion. If we make the conversion to a royalty-bearing license with respect to North America, then North America becomes part of the Royalty Territory. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any milestone or royalty payments from Cubist.

We have determined that the deliverables under the Cubist agreement include the licenses, technology transfer related to the ALN-RSV program, the joint steering committee and the development and manufacturing services that we are obligated to perform during the development period. We have determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the licenses and undelivered services are not separable and, accordingly, the licenses and services are being treated as a single unit of accounting. Under the Cubist agreement, the last element to be delivered is the development and manufacturing services, which have an expected life of approximately eight years. We are recognizing the upfront payment of \$20.0 million on a straight-line basis over approximately eight years because we are unable to reasonably estimate the level of effort to fulfill our performance obligations in order to utilize a proportional performance model. As future substantive milestones are achieved, a portion of the milestone payment, equal to the percentage of the performance period completed when the milestone is achieved, multiplied by the amount of the milestone payment, will be recognized as revenue upon achievement of such milestone. The remaining portion of the milestone will be recognized over the remaining performance period on a straight-line basis.

Under the terms of the Cubist agreement, we and Cubist share responsibility for developing licensed products in North America and each bears one-half of the related development costs, provided that under the terms of the November 2009 amendment, we are funding the advancement of ALN-RSV01 for adult lung transplant patients and Cubist retains an opt-in right. For revenue generating arrangements that involve cost sharing between both parties, we present the results of activities for which we 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, analogy to authoritative accounting literature or a reasonable, rational and consistently applied accounting policy election. As we are not considered the principal under the Cubist agreement, we record any amounts due from Cubist as a reduction of research and development expense.

**Government Contracts.** Revenue under government cost reimbursement contracts is recognized as we perform the underlying research and development activities.

***Accounting for Income Taxes***

In January 2007, we adopted a newly issued accounting standard which requires additional accounting and disclosure about uncertain tax positions. This standard clarifies the accounting for income tax positions by prescribing a minimum recognition threshold that a tax position is required to meet before being recognized in the financial statements. It also provides guidance on the derecognition of previously recognized deferred tax items, measurement, classification, interest and penalties, accounting in interim periods, disclosure and transition. Under this standard, we recognize the tax benefit from an uncertain tax position only if it is more likely than not that the tax position will be sustained upon examination by the taxing authorities, based on the technical merits of the tax position. The tax benefits recognized in our financial statements from such a position are measured based on the largest benefit that has a greater than 50% likelihood of being realized upon ultimate resolution.

We operate in the United States and Germany where our income tax returns are subject to audit and adjustment by local tax authorities. The nature of the uncertain tax positions is often very complex and subject to change and the

amounts at issue can be substantial. We develop our cumulative probability assessment of the measurement of uncertain tax positions using internal experience, judgment and assistance from professional advisors. Estimates are refined as additional information becomes known. Any outcome upon settlement that differs from our current estimate may result in additional tax expense in future periods.

**Table of Contents**

We recognize income taxes when transactions are recorded in our consolidated statements of operations, with deferred taxes provided for items that are recognized in different periods for financial statement and tax reporting purposes. We record a valuation allowance to reduce the deferred tax assets to the amount that is more likely than not to be realized. In addition, we estimate our exposures relating to uncertain tax positions and establish reserves for such exposures when they become probable and reasonably estimable.

For the years ended December 31, 2009 and 2008, we recorded a provision for income taxes of \$0.6 million and \$0.7 million, respectively. We provide income tax expense for federal alternative minimum tax, state and foreign taxes. We generated U.S. taxable income during 2009 and 2008 due to the recognition of certain proceeds received from the Roche and Takeda alliances. Our 2009 and 2008 U.S. taxable income will be offset by net operating loss carryforwards and other deferred tax attributes. However, we were subject to federal alternative minimum tax and state income taxes in 2009 and 2008.

At December 31, 2009, we had a valuation allowance against our net deferred tax assets to the extent it is more likely than not that the assets will not be realized. At December 31, 2009, we had utilized all federal and Massachusetts state net operating loss carryforwards and all foreign tax credits. At December 31, 2009, we had \$2.2 million of state research and development tax credit carryforwards derived from stock option exercises that are available to reduce future Massachusetts tax liabilities. At December 31, 2009, the California state net operating loss carryforward was \$8.6 million (related to Regulus, located in California). We have placed a valuation allowance against the state net operating loss and state credit deferred tax assets as it is unlikely that we will realize these assets. Ownership changes, as defined in the Internal Revenue Code, including those resulting from the issuance of common stock in connection with our 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. We have determined that there is no limitation on the utilization of net operating loss and tax credit carryforwards in accordance with Section 382 of the Internal Revenue Code in 2009.

***Accounting for Stock-Based Compensation***

Effective January 1, 2006, we adopted a newly issued accounting standard addressing recognition and disclosure of stock compensation. We adopted the fair value recognition provisions of this standard, using the modified prospective transition method. All stock-based awards granted to non-employees are accounted for at their fair value and compensation expense is generally recognized over the vesting period of the award. Determining the amount of stock-based compensation to be recorded requires us to develop estimates of fair values of stock options as of the grant date. We calculate the grant date fair values using the Black-Scholes valuation model. Our expected stock price volatility assumption is based on a combination of the historical and implied volatility of our publicly traded stock. For stock option grants issued during the year ended December 31, 2009, we used a weighted-average expected stock-price volatility assumption of 56%. Our expected life assumption is based on the equal weighting of our historical data and the historical data of our pharmaceutical and biotechnology peers. Our weighted average expected term was 6.2 years for the year ended December 31, 2009. We utilize a dividend yield of zero based on the fact that we have never paid cash dividends and have no present intention to pay cash dividends. The risk-free interest rate used for each grant is based on the U.S. Treasury yield curve in effect at the time of grant for instruments with a similar expected life.

As of December 31, 2009, the estimated fair value of unvested employee awards was \$44.7 million, net of estimated forfeitures. This amount will be recognized over the weighted average remaining vesting period of approximately 1.5 years for these awards. Stock-based employee compensation expense was \$18.9 million for the year ended December 31, 2009. However, the total amount of stock-based compensation expense recognized in any future period cannot be predicted at this time because it will depend on levels of stock-based payments granted in the future as well as the portion of the awards that actually vest. The stock compensation accounting standard requires forfeitures to be

estimated at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from those estimates. The term forfeitures is distinct from cancellations or expirations and represents only the unvested portion of the surrendered option. We currently expect, based on an analysis of our historical forfeitures, that approximately 83% of our options will actually vest, and therefore have applied an annual



**Table of Contents**

forfeiture rate of 4.5% to all unvested options as of December 31, 2009. Ultimately, the actual expense recognized over the vesting period will only be for those shares that vest.

***Accounting for Joint Venture***

We account for our interest in Regulus using the equity method of accounting. We reviewed the consolidation guidance that defines a variable interest entity, or VIE, and concluded that Regulus currently qualifies as a VIE. The founding investor rights agreement contains transfer restrictions on each of Isis and our interests and, as a result, we and Isis are considered related parties. Because we and Isis are related parties and collectively own 100% of Regulus, the determination of which entity would be considered the primary beneficiary is based on which entity is most closely associated with Regulus. Following consolidation guidance, we have concluded that Isis is the primary beneficiary and, accordingly, we have not consolidated Regulus and account for our investment under the equity method of accounting. Under new consolidation guidance effective January 1, 2010, we do not expect Isis to continue to consolidate Regulus.

***Estimated Liability for Development Costs***

We record accrued liabilities related to expenses for which service providers have not yet billed us with respect to products or services that we have received, specifically related to ongoing pre-clinical studies and clinical trials. These costs primarily relate to third-party clinical management costs, laboratory and analysis costs, toxicology studies and investigator fees. We have multiple product candidates in concurrent pre-clinical studies and clinical trials at multiple clinical sites throughout the world. In order to ensure that we have adequately provided for ongoing pre-clinical and clinical development costs during the period in which we incur such costs, we maintain an accrual to cover these expenses. We update our estimate for this accrual on at least a quarterly basis. The assessment of these costs is a subjective process that requires judgment. Upon settlement, these costs may differ materially from the amounts accrued in our consolidated financial statements. Our historical accrual estimates have not been materially different from our actual amounts.

**Results of Operations**

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

	<b>Year Ended December 31,</b>		
	<b>2009</b>	<b>2008</b>	<b>2007</b>
Net revenues from research collaborators	\$ 100,533	\$ 96,163	\$ 50,897
Operating expenses	148,644	123,998	144,074
Loss from operations	(48,111)	(27,835)	(93,177)
Net loss	\$ (47,590)	\$ (26,249)	\$ (85,466)

**Discussion of Results of Operations for 2009 and 2008**

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

**Year Ended  
December 31,**

	<b>2009</b>	<b>2008</b>
Roche	\$ 56,884	\$ 54,427
Takeda	21,732	12,794
Novartis	9,811	11,635
Government contract	7,471	14,172
Other research collaborator	3,593	928
InterfeRx program, research reagent license and other	1,042	2,207
<b>Total net revenues from research collaborators</b>	<b>\$ 100,533</b>	<b>\$ 96,163</b>

**Table of Contents**

Revenues increased for the year ended December 31, 2009 as compared to the year ended December 31, 2008 primarily as a result of a full year of revenues from our May 2008 alliance with Takeda. We are recognizing as revenue the \$150.0 million in upfront and technology transfer milestone payments made or due to us under the Takeda alliance on a straight-line basis over seven years, which equates to approximately \$5.0 million per quarter. Also contributing to the increase in 2009 were higher revenues under the Roche alliance related primarily to a development milestone achieved in 2009. Under the Roche alliance, we are recognizing revenue on a straight-line basis over five years, which equates to approximately \$14.0 million per quarter.

The decrease in Novartis revenues during the year ended December 31, 2009 as compared to the year ended December 31, 2008 was due in part to a reduction in the number of resources allocated to the broad Novartis alliance. The Novartis collaboration and related portion of Novartis revenues are currently expected to end in the fourth quarter of 2010. The Novartis collaboration and license agreement provides Novartis with a non-exclusive option to integrate into its operations our intellectual property relating to RNAi technology, excluding any technology related to delivery of nucleic acid based molecules. Novartis may exercise this integration option at any point during the research term. In connection with the exercise of the integration option, Novartis would be required to make additional payments to us totaling \$100.0 million, payable in full at the time of exercise, which payments would include an option exercise fee, a milestone based on the overall success of the collaboration, and pre-paid milestones and royalties that could become due as a result of future development of products using our technology. Novartis' exercise of this integration option would increase revenues substantially.

For the year ended December 31, 2009 as compared to the year ended December 31, 2008, government contract revenues decreased primarily as a result of the wind down of our collaboration with DTRA. Following a program review, in February 2009, we and DTRA determined not to continue this program and accordingly, the remaining funds were not accessed.

Other research collaborator revenues increased in the year ended December 31, 2009 as compared to the year ended December 31, 2008 due primarily to our alliance with Cubist. In consideration for the rights granted to Cubist under the agreement, in January 2009, Cubist paid us an upfront cash payment of \$20.0 million. We are recognizing this \$20.0 million payment as revenue on a straight-line basis over approximately eight years.

The decrease in InterfeRx program, research reagent license and other revenues for the year ended December 31, 2009 compared to the prior year was due to milestone payments from certain InterfeRx licensees received in 2008.

Total deferred revenue of \$271.8 million at December 31, 2009 consists of payments received from collaborators, primarily Roche, Takeda, Kyowa Hakko Kirin and Cubist, 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, Novartis and Cubist, as well as other strategic alliances, collaborations, government and foundation funding, and licensing activities.

***Operating Expenses***

The following table summarizes 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:

<b>% of Total</b>	<b>% of Total</b>
-----------------------	-----------------------

	<b>2009</b>	<b>Operating Expenses</b>	<b>2008</b>	<b>Operating Expenses</b>	<b>Increase \$</b>	<b>%</b>
Research and development	\$ 108,730	73%	\$ 96,883	78%	\$ 11,847	12%
General and administrative	39,914	27%	27,115	22%	12,799	47%
<b>Total operating expenses</b>	<b>\$ 148,644</b>	<b>100%</b>	<b>\$ 123,998</b>	<b>100%</b>	<b>\$ 24,646</b>	<b>20%</b>

**Table of Contents**

**Research and development.** The following table summarizes 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:

	<b>2009</b>	<b>% of Expense Category</b>	<b>2008</b>	<b>% of Expense Category</b>	<b>Increase (Decrease) \$</b>	<b>%</b>
<b>Research and development</b>						
Compensation and related	\$ 21,632	20%	\$ 17,664	18%	\$ 3,968	22%
External services	20,642	19%	22,852	24%	(2,210)	(10)%
Clinical trial and manufacturing	18,880	17%	13,342	14%	5,538	42%
License fees	13,632	13%	12,624	13%	1,008	8%
Facilities-related	11,612	11%	10,439	11%	1,173	11%
Non-cash stock-based compensation	11,415	10%	9,575	10%	1,840	19%
Lab supplies and materials	8,106	7%	8,095	8%	11	*
Other	2,811	3%	2,292	2%	519	23%
<b>Total research and development expenses</b>	<b>\$ 108,730</b>	<b>100%</b>	<b>\$ 96,883</b>	<b>100%</b>	<b>\$ 11,847</b>	<b>12%</b>

\* Indicates less than 1%

Research and development expenses increased during the year ended December 31, 2009 due primarily to increased clinical program and manufacturing expenses associated with our ALN-TTR pre-clinical program and our ALN-VSP clinical trial. Also contributing to the increase in research and development expenses for the year ended December 31, 2009 was an increase in compensation and related, non-cash stock-based compensation and facilities-related expenses due primarily to additional research and development headcount to support our alliances and expanding product pipeline. Partially offsetting these increases, external services expenses decreased during the year ended December 31, 2009 as a result of lower pre-clinical activities due primarily to the wind down of our collaboration with DTRA. In addition, under the terms of our January 2009 agreement with Cubist, we and Cubist each were responsible for one-half of the development costs for our ALN-RSV program through November 2009. In November 2009, we and Cubist agreed to focus our collaboration and joint development efforts on ALN-RSV02 for use in pediatric patients. In turn, Alnylam is funding the advancement of ALN-RSV01 for adult lung transplant patients and Cubist retains an opt-in right. For the year ended December 31, 2009, we recorded amounts due from Cubist of \$5.3 million as a reduction to research and development expenses.

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 in 2010 as we continue development of our and our collaborators' product candidates and focus on continuing to develop drug delivery-related technologies.

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 our most-advanced programs are in the early stages of clinical 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.

**Table of Contents**

**General and administrative.** The following table summarizes 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:

	<b>2009</b>	<b>% of Expense Category</b>	<b>2008</b>	<b>% of Expense Category</b>	<b>Increase (Decrease) \$</b>	<b>%</b>
<b>General and administrative</b>						
Consulting and professional services	\$ 19,903	50%	\$ 9,281	34%	\$ 10,622	114%
Non-cash stock-based compensation	8,312	21%	6,807	25%	1,505	22%
Compensation and related	6,383	16%	5,763	21%	620	11%
Facilities-related	2,634	7%	2,401	9%	233	10%
Insurance	747	2%	682	3%	65	10%
Other	1,935	4%	2,181	8%	(246)	(11)%
<b>Total general and administrative expenses</b>	<b>\$ 39,914</b>	<b>100%</b>	<b>\$ 27,115</b>	<b>100%</b>	<b>\$ 12,799</b>	<b>47%</b>

The increase in general and administrative expenses during the year ended December 31, 2009 was due primarily to higher consulting and professional services expenses related to business activities, primarily legal activities, a description of which is set forth in Part I, Item 3 of this annual report on Form 10-K. Also contributing to the increase were higher non-cash stock-based compensation and compensation and related expenses due to a modest increase in general and administrative headcount over the past year to support our growth. We expect that general and administrative expenses, excluding expenses associated with legal activities, will remain consistent or increase slightly in 2010.

**Other income (expense)**

We incurred \$4.9 million equity in loss of joint venture (Regulus Therapeutics Inc.) for the year ended December 31, 2009 as compared to \$9.3 million for the year ended December 31, 2008 related to our share of the net losses incurred by Regulus. Through December 31, 2008, we were recognizing the first \$10.0 million of losses of Regulus as equity in loss of joint venture (Regulus Therapeutics Inc.) in our consolidated statements of operations because we were responsible for funding those losses through our initial \$10.0 million cash contribution. Beginning in January 2009, in connection with the conversion of Regulus to a C corporation, we are recognizing approximately 49% of the income and losses of Regulus. The carrying value of our investment in joint venture (Regulus Therapeutics Inc.) immediately prior to the conversion to a C corporation exceeded 49% of the net assets of Regulus by approximately \$0.8 million. Upon conversion, this amount was allocated to the intellectual property of Regulus and, because the intellectual property was determined to be in-process research and development, the \$0.8 million was recorded as a charge to expense. This charge is included in equity in loss of joint venture (Regulus Therapeutics Inc.) in the consolidated statements of operations for the year ended December 31, 2009. Separate financial information for Regulus is included in Exhibit 99.1 to this annual report on Form 10-K.

Interest income was \$5.4 million in 2009 as compared to \$14.4 million in 2008. The decrease in 2009 was due primarily to significantly lower average interest rates.

Interest expense was zero in 2009 as compared to \$0.9 million in 2008. Interest expense in 2008 was related to borrowings under our lines of credit used to finance capital equipment purchases. In December 2008, we repaid the aggregate outstanding balance under these credit lines.

Other income was \$0.6 million in 2009 as compared to other expense of \$1.9 million in 2008. Other income in 2009 consisted primarily of realized gains on sales of marketable securities. Included in other expense in 2008 was 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.

Income taxes, primarily as a result of our alliances with Roche and Takeda, was a provision for income taxes of \$0.6 million and \$0.7 million for the years ended December 31, 2009 and 2008, respectively.



**Table of Contents****Discussion of Results of Operations for 2008 and 2007**

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

	<b>Year Ended December 31,</b>	
	<b>2008</b>	<b>2007</b>
Roche	\$ 54,427	\$ 17,571
Government contract	14,172	9,800
Takeda	12,794	
Novartis	11,635	14,670
InterfeRx program, research reagent license and other	2,207	1,526
Other research collaborator	928	7,330
<b>Total net revenues from research collaborators</b>	<b>\$ 96,163</b>	<b>\$ 50,897</b>

Revenues increased significantly for the year ended December 31, 2008 as compared to the year ended December 31, 2007 primarily as a result of our August 2007 alliance with Roche, as well as our May 2008 alliance with Takeda. Under the Roche alliance, \$278.2 million was being recognized as revenue on a straight-line basis over five years, which equates to approximately \$14.0 million per quarter. In connection with the Roche alliance, 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) \$1.0 million and \$4.2 million for these services during the years ended December 31, 2008 and 2007, respectively. Under the Takeda alliance, the \$150.0 million in upfront and technology transfer milestone payments made or due to us are being recognized as revenue on a straight-line basis over seven years, which equates to approximately \$5.0 million per quarter.

For the year ended December 31, 2008 as compared to the year ended December 31, 2007, government contract revenues increased primarily as a result of our collaboration with DTRA, which began in the third quarter of 2007.

The increase in InterfeRx program, research reagent license and other revenues for the year ended December 31, 2008 compared to the prior year was due to milestone payments from certain InterfeRx licensees received in 2008.

The decrease in Novartis revenues during the year ended December 31, 2008 as compared to the year ended December 31, 2007 was due in part to the wind down of the Novartis flu alliance.

Other research collaborator revenues decreased in the year ended December 31, 2008 as compared to the year ended December 31, 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 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.



**Table of Contents****Operating Expenses**

The following table summarizes 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:

	2008	% of Total Operating Expenses	2007	% of Total Operating Expenses	Increase (Decrease) \$	%
Research and development	\$ 96,883	78%	\$ 120,686	84%	\$ (23,803)	(20)%
General and administrative	27,115	22%	23,388	16%	3,727	16%
<b>Total operating expenses</b>	<b>\$ 123,998</b>	<b>100%</b>	<b>\$ 144,074</b>	<b>100%</b>	<b>\$ (20,076)</b>	<b>(14)%</b>

**Research and development.** The following table summarizes 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:

	2008	% of Expense Category	2007	% of Expense Category	Increase (Decrease) \$	%
<b>Research and development</b>						
External services	\$ 22,852	24%	\$ 18,417	15%	\$ 4,435	24%
Compensation and related	17,664	18%	13,201	11%	4,463	34%
Clinical trial and manufacturing	13,342	14%	20,662	17%	(7,320)	(35)%
License fees	12,624	13%	42,207	35%	(29,583)	(70)%
Facilities-related	10,439	11%	8,511	7%	1,928	23%
Non-cash stock-based compensation	9,575	10%	9,363	8%	212	2%
Lab supplies and materials	8,095	8%	6,154	5%	1,941	32%
Other	2,292	2%	2,171	2%	121	6%
<b>Total research and development expenses</b>	<b>\$ 96,883</b>	<b>100%</b>	<b>\$ 120,686</b>	<b>100%</b>	<b>\$ (23,803)</b>	<b>(20)%</b>

Research and development expenses decreased during the year ended December 31, 2008 as compared to the year ended December 31, 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 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 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 Tekmira license agreement and \$3.2 million associated with various intellectual property assets.

Clinical trial and manufacturing expenses decreased during the year ended December 31, 2008 as compared to the year ended December 31, 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 year ended December 31, 2008 as compared to the year ended December 31, 2007 as a result of higher expenses related to our government programs, our RSV program and our pre-clinical programs for the treatment of liver cancer and HD, 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 year ended December 31, 2008 as compared to the prior year due to additional research and development headcount to support our alliances and expanding product pipeline.

**Table of Contents**

**General and administrative.** The following table summarizes 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:

	<b>2008</b>	<b>% of Expense Category</b>	<b>2007</b>	<b>% of Expense Category</b>	<b>Increase (Decrease)</b>	
					<b>\$</b>	<b>%</b>
<b>General and administrative</b>						
Consulting and professional services	\$ 9,281	34%	\$ 8,547	36%	\$ 734	9%
Non-cash stock-based compensation	6,807	25%	5,109	22%	1,698	33%
Compensation and related	5,763	21%	4,647	20%	1,116	24%
Facilities-related	2,401	9%	2,486	11%	(85)	(3)%
Insurance	682	3%	654	3%	28	4%
Other	2,181	8%	1,945	8%	236	12%
<b>Total general and administrative expenses</b>	<b>\$ 27,115</b>	<b>100%</b>	<b>\$ 23,388</b>	<b>100%</b>	<b>\$ 3,727</b>	<b>16%</b>

The increase in general and administrative expenses during the year ended December 31, 2008 as compared to the prior year was due primarily to an increase in general and administrative headcount during 2008 to support our growth and higher non-cash stock-based compensation.

**Other income (expense)**

Equity in loss of joint venture (Regulus Therapeutics Inc.) was \$9.3 million and \$1.1 million during the years ended December 31, 2008 and 2007, respectively, related to our share of the net losses incurred by Regulus, which was formed in September 2007. The increase was a result of Regulus ramping up its operations throughout 2008. Separate financial information for Regulus is included in Exhibit 99.1 to this annual report on Form 10-K.

Interest income was \$14.4 million in 2008 as compared to \$15.4 million in 2007. The decrease was due to lower average interest rates during the year ended December 31, 2008, partially offset by higher average cash, cash equivalent and marketable securities balances.

Interest expense was \$0.9 million in 2008 as compared to \$1.1 million in 2007. Interest expense in each period was related to borrowings under our lines of credit used to finance capital equipment purchases. In December 2008, we repaid the aggregate outstanding balance under these credit lines.

Included in other expense during the year ended December 31, 2008 was 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.

Our provision for income taxes was \$0.7 million for year ended December 31, 2008 primarily as a result of our 2007 alliance with Roche. Income tax expense was \$5.2 million for the prior year primarily as a result of the sale of our German operations to Roche in August 2007 for \$15.0 million.



**Table of Contents****Liquidity and Capital Resources**

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

	<b>Year Ended December 31,</b>		
	<b>2009</b>	<b>2008</b>	<b>2007</b>
Net loss	\$ (47,590)	\$(26,249)	\$ (85,466)
Adjustments to reconcile net loss to net cash provided by (used in) operating activities	25,857	27,840	29,834
Changes in operating assets and liabilities	(50,412)	63,900	252,151
Net cash (used in) provided by operating activities	(72,145)	65,491	196,519
Net cash provided by (used in) investing activities	14,433	17,936	(277,425)
Net cash provided by financing activities	3,509	3,155	58,635
Effect of exchange rate on cash	(121)	53	(527)
Net (decrease) increase in cash and cash equivalents	(54,324)	86,635	(22,798)
Cash and cash equivalents, beginning of period	191,792	105,157	127,955
Cash and cash equivalents, end of period	\$ 137,468	\$191,792	\$ 105,157

Since we commenced operations in 2002, we have generated significant losses. As of December 31, 2009, we had an accumulated deficit of \$299.8 million. As of December 31, 2009, we had cash, cash equivalents and marketable securities of \$435.3 million, compared to cash, cash equivalents and marketable securities of \$512.7 million as of December 31, 2008. We invest primarily in cash equivalents, U.S. government and municipal 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 impairment charges to our fixed income marketable securities as of December 31, 2009.

***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 year ended December 31, 2009 compared to the year ended December 31, 2008 was due primarily to our net loss and other changes in our working capital. We had a decrease in deferred revenue of \$58.2 million for year ended December 31, 2009, partially offset by an increase in accounts payable of \$9.9 million. We had an increase in deferred revenue of \$66.7 million for the year ended December 31, 2008 due primarily to the proceeds received from our Takeda and Kyowa Hakko Kirin alliances. 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 (Regulus Therapeutics Inc.) and depreciation and amortization.

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

agreements or other strategic transactions, if any, and the timing and progress of our research and development efforts.

***Investing activities***

For the year ended December 31, 2009, net cash provided by investing activities of \$14.4 million resulted primarily from net sales and maturities of marketable securities of \$23.2 million and a decrease in restricted cash of \$6.2 million resulting from the release of letters of credit in connection with the amendment of our facility lease and the termination of our sublease agreement. Offsetting these amounts was a \$10.0 million investment in Regulus and purchases of property and equipment of \$4.9 million. For the year ended December 31, 2008, net cash provided by



**Table of Contents**

investing activities of \$17.9 million resulted primarily from net sales and maturities of marketable securities of \$28.8 million. Offsetting this amount was purchases of property and equipment of \$10.8 million.

***Financing activities***

For the year ended December 31, 2009, net cash provided by financing activities of \$3.5 million was due to proceeds of \$1.2 million from our issuance of common stock to Novartis in May 2009, as well as proceeds of \$2.4 million from the issuance of common stock in connection with stock option exercises. For the year ended December 31, 2008, net cash provided by financing activities was \$3.2 million due to proceeds of \$5.4 million from our issuance of common stock to Novartis in May 2008, as well as proceeds of \$4.5 million from the issuance of common stock in connection with stock option exercises, offset by \$6.8 million for repayments of notes payable.

In March 2006, we entered into an agreement with Oxford Finance Corp., 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. 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. On the maturity of each equipment advance under the Lighthouse line of credit, we were required to pay, in addition to the principal and interest due, an additional amount of 11.5% of the original principal. This amount was being accrued over the applicable borrowing period as additional interest expense. In December 2008, we repaid the aggregate outstanding balance under the Oxford and Lighthouse credit lines.

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. In addition, the current economic downturn has severely diminished the availability of capital and may limit our ability to access these markets to obtain financing in the future. Based on our current operating plan, we believe that our existing cash, cash equivalents and fixed income marketable securities, for which we have not recognized any impairment charges, together with the cash we expect to generate under our current alliances, including our Novartis, Roche, Takeda and Cubist 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, conduct 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 product candidates;

progress in our research and development programs, as well as the magnitude of these programs;

the timing, receipt and amount of milestone and other payments, if any, from present and future collaborators, if any;

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

**Table of Contents**

our ability to maintain and establish additional collaborative arrangements;

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

the resources, time and cost required for the preparation, filing, prosecution, maintenance and enforcement of patent claims;

the costs associated with legal activities arising in the course of our business activities;

progress in the research and development programs of Regulus; and

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

**Off-Balance Sheet Arrangements**

In connection with our license agreements with Max-Planck-Gesellschaft Zur Forderung Der Wissenschaften E.V. and Max-Planck-Innovation GmbH, collectively, Max Planck, relating to the Tuschl I and II patent applications, we are required to indemnify Max Planck for certain damages arising in connection with the intellectual property rights licensed under the agreements. Under this indemnification agreement with Max Planck, we are responsible for paying the costs of any litigation relating to the license agreements or the underlying intellectual property rights. These amounts are charged to general and administrative expense. In addition, we are a party to a number of agreements entered into in the ordinary course of business, which contain typical provisions that obligate us to indemnify the other parties to such agreements upon the occurrence of certain events. These indemnification obligations are considered off-balance sheet arrangements in accordance with GAAP. To date, other than the costs associated with the litigation described in Part I, Item 3 of this annual report on Form 10-K, which we are responsible for under our indemnification agreement with Max Planck, we have not encountered material costs as a result of such obligations and have not accrued any liabilities related to such obligations in our consolidated financial statements. See Note 7 to our consolidated financial statements included in this annual report on Form 10-K for further discussion of these indemnification agreements.

**Contractual Obligations**

In the table below, we set forth our enforceable and legally binding obligations and future commitments as of December 31, 2009, as well as obligations related to contracts that we are likely to continue, regardless of the fact that they were cancelable as of December 31, 2009. Some of the figures that we include in this table are based on management's estimate and assumptions about these obligations, including their duration, the possibility of renewal, anticipated actions by third parties, and other factors. Because these estimates and assumptions are necessarily subjective, the obligations we will actually pay in future periods may vary from those reflected in the table.

	<b>Payments Due by Period</b>				<b>Total</b>
	<b>2010</b>	<b>2011 and 2012</b>	<b>2013 and 2014</b>	<b>After 2014</b>	
<b>Contractual Obligations</b>					
Operating lease obligations(1)	\$ 3,727	\$ 7,725	\$ 8,385	\$ 7,878	\$ 27,715
Purchase commitments(2)	12,273	3,782			16,055

Edgar Filing: ALNYLAM PHARMACEUTICALS, INC. - Form 10-K

Technology-related commitments(3)	18,225	6,558	1,041	6,823	32,647
Total contractual cash obligations	\$ 34,225	\$ 18,065	\$ 9,426	\$ 14,701	\$ 76,417

- (1) Relates to our Cambridge, Massachusetts non-cancelable operating lease agreement.
- (2) Includes commitments related to purchase orders, clinical and pre-clinical agreements, and other purchase commitments for goods or services.
- (3) Relates to our fixed payment obligations under license agreements, as well as other payments related to technology research and development. Includes a potential \$10.0 million milestone payable to Isis during the fourth quarter. A description of the amended and restated Isis agreement is included above under Strategic Alliances Isis in this annual report on Form 10-K.

## **Table of Contents**

We in-license technology from a number of sources. Pursuant to these in-license agreements, we will be required to make additional payments if and when we achieve specified development and regulatory milestones. To the extent we are unable to reasonably predict the likelihood, timing or amount of such payments, we have excluded them from the table above.

### **Recent Accounting Pronouncements**

In June 2009, the Financial Accounting Standards Board, or FASB, issued the FASB Accounting Standards Codification, or ASC. Effective in the third quarter of 2009, the ASC became the single source for all authoritative GAAP recognized by the FASB, and is required to be applied to financial statements issued for interim and annual periods ending after September 15, 2009. The ASC does not change GAAP and did not impact our consolidated financial statements.

In October 2009, the FASB issued a new accounting standard, which amends existing revenue recognition accounting pronouncements and provides accounting principles and application guidance on whether multiple deliverables exist, how the arrangement should be separated and the consideration allocated. This standard eliminates the requirement to establish the fair value of undelivered products and services and instead provides for separate revenue recognition based upon management's estimate of the selling price for an undelivered item when there is no other means to determine the fair value of that undelivered item. Previously, accounting principles required that the fair value of the undelivered item be the price of the item either sold in a separate transaction between unrelated third parties or the price charged for each item when the item is sold separately by the vendor. This was difficult to determine when the product was not individually sold because of its unique features. If the fair value of all of the elements in the arrangement was not determinable, then revenue was deferred until all of the items were delivered or fair value was determined. This new approach is effective prospectively for revenue arrangements entered into or materially modified in fiscal years beginning on or after June 15, 2010. We are currently evaluating the potential impact of this accounting standard on our consolidated financial statements.

In June 2009, the FASB issued a new accounting standard, which has not yet been integrated into the ASC. Accordingly, it will remain authoritative until integrated. Statement of Financial Accounting Standards, or SFAS, No. 167, Amendments to FASB Interpretation No. 46(R), or SFAS 167, amends previously issued accounting guidance for the consolidation of a VIE to require an enterprise to determine whether its variable interest or interests give it a controlling financial interest in a VIE. This amended consolidation guidance for VIEs also replaces the existing quantitative approach for identifying which enterprise should consolidate a VIE, which was based on which enterprise was exposed to a majority of the risks and rewards, with a qualitative approach, based on which enterprise has both (1) the power to direct the economically significant activities of the entity and (2) the obligation to absorb losses of the entity that could potentially be significant to the VIE or the right to receive benefits from the entity that could potentially be significant to the VIE. This new accounting standard has broad implications and may affect how we account for the consolidation of common structures, such as joint ventures, equity method investments, collaboration and other agreements, and purchase arrangements. Under this revised consolidation guidance, more entities may meet the definition of a VIE, and the determination about who should consolidate a VIE is required to be evaluated continuously. We have completed our evaluation of the impact of adopting this standard and determined that the adoption will not have an impact on our consolidated financial statements.

**Table of Contents**

**ITEM 7A. 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 and municipal 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 sensitive to changes in interest rates and changes in the credit ratings of the issuers. Interest rate changes would result in a change in the net fair value of these financial instruments due to the difference between the market interest rate and the market interest rate at the date of purchase of the financial instrument. If market interest rates were to increase immediately and uniformly by 50 basis points, or one-half of a percentage point, from levels at December 31, 2009, the net fair value of our interest-sensitive financial instruments would have resulted in a hypothetical decline of \$1.6 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 impairment charges to our fixed income marketable securities as of December 31, 2009.

**ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA**

**INDEX TO CONSOLIDATED FINANCIAL STATEMENTS**

	<b>Page</b>
<u>Management's Annual Report on Internal Control Over Financial Reporting</u>	103
<u>Report of Independent Registered Public Accounting Firm</u>	104
<u>Consolidated Balance Sheets as of December 31, 2009 and 2008</u>	105
<u>Consolidated Statements of Operations and Comprehensive Loss for the Years Ended December 31, 2009, 2008 and 2007</u>	106
<u>Consolidated Statements of Stockholders' Equity for the Years Ended December 31, 2007, 2008 and 2009</u>	107
<u>Consolidated Statements of Cash Flows for the Years Ended December 31, 2009, 2008 and 2007</u>	108
<u>Notes to Consolidated Financial Statements</u>	109

**Table of Contents**

**Management's Annual Report on Internal Control Over Financial Reporting**

The management of the Company is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rule 13a-15(f) or 15d-15(f) promulgated under the Securities Exchange Act of 1934 as a process designed by, or under the supervision of, the company's principal executive and principal financial officers and effected by the company's board of directors, management and other personnel, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles and includes those policies and procedures that:

Pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of the assets of the Company;

Provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the Company are being made only in accordance with authorizations of management and directors of the Company; and

Provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of the Company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

The Company's management assessed the effectiveness of the Company's internal control over financial reporting as of December 31, 2009. In making this assessment, the Company's management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in Internal Control-Integrated Framework.

Based on our assessment, management concluded that, as of December 31, 2009, the Company's internal control over financial reporting is effective based on those criteria.

The effectiveness of the Company's internal control over financial reporting as of December 31, 2009 has been audited by PricewaterhouseCoopers LLP, an independent registered public accounting firm, as stated in their report. This report appears on page 104.



**Table of Contents**

**Report of Independent Registered Public Accounting Firm**

To the Board of Directors and Stockholders of Alnylam Pharmaceuticals, Inc.:

In our opinion, based on our audits and the report of other auditors, the accompanying consolidated balance sheets and the related consolidated statements of operations and comprehensive loss, stockholders' equity and cash flows present fairly, in all material respects, the financial position of Alnylam Pharmaceuticals, Inc. and its subsidiaries at December 31, 2009 and 2008, and the results of their operations and their cash flows for each of the three years in the period ended December 31, 2009 in conformity with accounting principles generally accepted in the United States of America. Also in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2009, based on criteria established in Internal Control - Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). The Company's management is responsible for these financial statements, for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting, included in Management's Annual Report on Internal Control over Financial Reporting. Our responsibility is to express opinions on these financial statements and on the Company's internal control over financial reporting based on our integrated audits. We did not audit the financial statements of Regulus Therapeutics Inc., an approximate 49 percent-owned equity investment, which were audited by other auditors whose report thereon has been furnished to us. Our opinion expressed herein, insofar as it relates to the Company's net investment in (approximately \$6.4 million and \$1.6 million at December 31, 2009 and 2008, respectively) and equity in the net loss (approximately \$4.9 million, \$9.3 million and \$1.1 million for the year ended December 31, 2009 and 2008 and for the period from September 6, 2007 (inception) to December 31, 2007, respectively) of Regulus Therapeutics Inc., is based solely on the report of the other auditors. We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the financial statements are free of material misstatement and whether effective internal control over financial reporting was maintained in all material respects. Our audits of the financial statements included examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audits also included performing such other procedures as we considered necessary in the circumstances. We believe that our audits and the report of other auditors provide a reasonable basis for our opinions.

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ PricewaterhouseCoopers LLP

Boston, Massachusetts

February 26, 2010

**Table of Contents****ALNYLAM PHARMACEUTICALS, INC.****CONSOLIDATED BALANCE SHEETS****(In thousands, except share and per share amounts)**

	<b>December 31,</b>	
	<b>2009</b>	<b>2008</b>
<b>ASSETS</b>		
<b>Current assets:</b>		
Cash and cash equivalents	\$ 137,468	\$ 191,792
Marketable securities	143,934	238,596
Collaboration receivables	6,044	4,188
Prepaid expenses and other current assets	4,151	4,674
Deferred tax assets	1,937	875
Restricted cash		2,999
Total current assets	293,534	443,124
Marketable securities	153,914	82,321
Property and equipment, net	18,324	19,194
Deferred tax assets, net of current portion	8,556	4,507
Investment in joint venture (Regulus Therapeutics Inc.)	6,435	1,583
Intangible assets, net	622	795
Restricted cash, net of current portion		3,152
Total assets	\$ 481,385	\$ 554,676
<b>LIABILITIES AND STOCKHOLDERS EQUITY</b>		
<b>Current liabilities:</b>		
Accounts payable	\$ 12,489	\$ 2,588
Accrued expenses	9,833	9,328
Income taxes payable	5,644	6,111
Deferred rent	838	1,561
Deferred revenue	81,929	79,864
Total current liabilities	110,733	99,452
Deferred rent, net of current portion	2,609	2,732
Deferred revenue, net of current portion	189,884	250,121
Other long-term liabilities	194	246
Total liabilities	303,420	352,551

Commitments and contingencies (Notes 7 and 12)

**Stockholders equity:**

Preferred stock, \$0.01 par value, 5,000,000 shares authorized and no shares issued and outstanding at December 31, 2009 and 2008

Common stock, \$0.01 par value, 125,000,000 shares authorized; 41,837,427 shares issued and outstanding at December 31, 2009; 41,413,828 shares issued and outstanding at December 31, 2008

	418	414
Additional paid-in capital	476,663	452,767
Accumulated other comprehensive income	716	1,186
Accumulated deficit	(299,832)	(252,242)
Total stockholders equity	177,965	202,125
Total liabilities and stockholders equity	\$ 481,385	\$ 554,676

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

Table of Contents**ALNYLAM PHARMACEUTICALS, INC.****CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS****(In thousands, except per share amounts)**

	<b>Year Ended December 31,</b>		
	<b>2009</b>	<b>2008</b>	<b>2007</b>
<b>Net revenues from research collaborators</b>	\$ 100,533	\$ 96,163	\$ 50,897
<b>Operating expenses:</b>			
Research and development(1)	108,730	96,883	120,686
General and administrative(1)	39,914	27,115	23,388
Total operating expenses	148,644	123,998	144,074
Loss from operations	(48,111)	(27,835)	(93,177)
<b>Other income (expense):</b>			
Equity in loss of joint venture (Regulus Therapeutics Inc.)	(4,910)	(9,290)	(1,075)
Interest income	5,385	14,414	15,393
Interest expense		(872)	(1,083)
Other income (expense)	628	(1,947)	(279)
Total other income (expense)	1,103	2,305	12,956
Loss before income taxes	(47,008)	(25,530)	(80,221)
Provision for income taxes	(582)	(719)	(5,245)
Net loss	\$ (47,590)	\$ (26,249)	\$ (85,466)
Net loss per common share basic and diluted	\$ (1.14)	\$ (0.64)	\$ (2.21)
Weighted average common shares used to compute basic and diluted net loss per common share	41,633	41,077	38,657
<b>Comprehensive loss:</b>			
Net loss	\$ (47,590)	\$ (26,249)	\$ (85,466)
Foreign currency translation	(121)	53	(598)
Unrealized (loss) gain on marketable securities	(349)	833	258
Comprehensive loss	\$ (48,060)	\$ (25,363)	\$ (85,806)

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

Research and development	\$ 11,415	\$ 9,575	\$ 9,363
General and administrative	8,312	6,807	5,109

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

Table of Contents

## ALNYLAM PHARMACEUTICALS, INC.

## CONSOLIDATED STATEMENTS OF STOCKHOLDERS EQUITY

(In thousands, except share amounts)

	Common Stock Shares	Common Stock Amount	Additional Paid-in Capital	Deferred Stock-based Compensation	Accumulated Other Comprehensive Income	Accumulated Deficit	Total Stockholders Equity
<b>Balance at December 31, 2006</b>	37,050,631	\$ 371	\$ 340,779	\$ (89)	\$ 640	\$ (140,527)	\$ 201,174
Exercise of common stock options	1,247,808	12	9,232				9,244
Issuance of common stock	2,474,528	25	59,874				59,899
Stock-based compensation expense			14,364	89			14,453
Foreign currency translation					(598)		(598)
Joint venture stock-based compensation (Regulus Therapeutics Inc.)			204				204
Unrealized gain on marketable securities					258		258
Net loss						(85,466)	(85,466)
<b>Balance at December 31, 2007</b>	40,772,967	408	424,453		300	(225,993)	199,168
Exercise of common stock options	377,228	4	3,782				3,786
Issuance of common stock	263,633	2	6,507				6,509
Stock-based compensation expense			16,381				16,381
Foreign currency translation					53		53

Joint venture stock-based compensation (Regulus Therapeutics Inc.)			1,644				1,644
Unrealized gain on marketable securities					833		833
Net loss						(26,249)	(26,249)
<b>Balance at December 31, 2008</b>	41,413,828	414	452,767		1,186	(252,242)	202,125
Exercise of common stock options	275,908	3	1,459				1,462
Issuance of common stock	147,691	1	2,507				2,508
Stock-based compensation expense			19,727				19,727
Foreign currency translation					(121)		(121)
Joint venture stock-based compensation (Regulus Therapeutics Inc.)			(238)				(238)
Tax benefit from stock-based compensation			441				441
Unrealized loss on marketable securities					(349)		(349)
Net loss						(47,590)	(47,590)
<b>Balance at December 31, 2009</b>	41,837,427	\$ 418	\$ 476,663	\$	\$ 716	\$ (299,832)	\$ 177,965

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



**Table of Contents****ALNYLAM PHARMACEUTICALS, INC.****CONSOLIDATED STATEMENTS OF CASH FLOWS****(In thousands)**

	<b>Year Ended December 31,</b>		
	<b>2009</b>	<b>2008</b>	<b>2007</b>
<b>Cash flows from operating activities:</b>			
Net loss	\$ (47,590)	\$ (26,249)	\$ (85,466)
Adjustments to reconcile net loss to net cash provided by (used in) operating activities:			
Depreciation and amortization	5,992	5,726	4,082
Deferred income taxes	(5,163)	(5,501)	1,889
Non-cash stock-based compensation	19,727	18,026	14,676
Non-cash license expense			7,909
Charge for 401(k) company stock match	461	382	407
Equity in loss of joint venture (Regulus Therapeutics Inc.)	4,910	7,646	871
Tax benefit from stock-based compensation	441		
Impairment on equity investment		1,561	
Realized gain on sale of marketable securities	(511)		
Changes in operating assets and liabilities:			
Proceeds from landlord tenant improvements		581	2,621
Collaboration receivables	(1,856)	843	(1,194)
Prepaid expenses and other assets	523	(1,748)	(4,348)
Accounts payable	9,901	(1,238)	(264)
Income taxes payable	(467)	2,614	3,497
Accrued expenses and other	(341)	(3,821)	6,843
Deferred revenue	(58,172)	66,669	244,996
Net cash (used in) provided by operating activities	(72,145)	65,491	196,519
<b>Cash flows from investing activities:</b>			
Purchases of property and equipment	(4,949)	(10,764)	(7,788)
Disposals of property and equipment			2,342
Decrease (increase) in restricted cash	6,151		(839)
Purchases of marketable securities	(481,339)	(482,244)	(544,394)
Sales and maturities of marketable securities	504,570	511,044	283,254
Investment in joint venture (Regulus Therapeutics Inc.)	(10,000)	(100)	(10,000)
Net cash provided by (used in) investing activities	14,433	17,936	(277,425)
<b>Cash flows from financing activities:</b>			
Proceeds from issuance of common stock	2,355	4,505	61,011

Edgar Filing: ALNYLAM PHARMACEUTICALS, INC. - Form 10-K

Proceeds from issuance of shares to Novartis	1,154	5,408	
Proceeds from notes payable			957
Repayments of notes payable		(6,758)	(3,333)
Net cash provided by financing activities	3,509	3,155	58,635
Effect of exchange rate on cash	(121)	53	(527)
Net (decrease) increase in cash and cash equivalents	(54,324)	86,635	(22,798)
Cash and cash equivalents, beginning of period	191,792	105,157	127,955
Cash and cash equivalents, end of period	\$ 137,468	\$ 191,792	\$ 105,157
<b>Supplemental disclosure of cash flows</b>			
Cash paid for interest	\$	\$ 1,499	\$ 890
Cash paid for income taxes, net	\$ 5,836	\$ 2,671	\$
<b>Supplemental disclosure of non-cash financing activities</b>			
Common stock issued in connection with license agreements	\$	\$	\$ 7,909

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

**Table of Contents**

**ALNYLAM PHARMACEUTICALS, INC.**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS**

**1. NATURE OF BUSINESS**

Alnylam Pharmaceuticals, Inc. (the Company or Alnylam ) commenced operations on June 14, 2002 as a biopharmaceutical company seeking to develop and commercialize novel therapeutics based on RNA interference ( RNAi ). Alnylam is focused on discovering, developing and commercializing RNAi therapeutics by establishing strategic alliances with leading pharmaceutical and biotechnology companies, establishing and maintaining a strong intellectual property position in the RNAi field, generating revenues through licensing agreements and ultimately developing and commercializing RNAi therapeutics for its own account. The Company has devoted substantially all of its efforts to business planning, research and development, acquiring, filing and expanding intellectual property rights, recruiting management and technical staff, and raising capital.

**2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES**

***Basis of Presentation and Principles of Consolidation***

The Company comprises four entities, Alnylam Pharmaceuticals, Inc. (the parent company) and three wholly-owned subsidiaries (Alnylam U.S., Inc., Alnylam Europe AG ( Alnylam Europe ) and Alnylam Securities Corporation). Alnylam Pharmaceuticals, Inc. is a Delaware corporation that was formed on May 8, 2003. Alnylam U.S., Inc. is also a Delaware corporation that was formed on June 14, 2002. Alnylam Securities Corporation is a Massachusetts corporation that was formed on December 19, 2006. Alnylam Europe was incorporated in Germany in June 2000 under the name Ribopharma AG. The Company acquired Alnylam Europe in July 2003.

The accompanying consolidated financial statements reflect the operations of the Company and its wholly-owned subsidiaries. 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 Inc., formerly Regulus Therapeutics LLC ( Regulus ).

***Reclassifications***

Certain reclassifications have been made to prior years consolidated financial statements to conform to the 2009 presentation.

***Use of Estimates***

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

***Concentrations of Credit Risk and Significant Customers***

Financial instruments which potentially expose the Company to concentrations of credit risk consist primarily of cash, cash equivalents and marketable securities. As of December 31, 2009 and 2008, substantially all of the Company's cash, cash equivalents and marketable securities were invested in money market mutual funds, commercial paper, corporate notes, and U.S. government and municipal securities through highly rated financial institutions.

To date, the Company's revenues from collaborations have been generated from primarily F. Hoffmann-La Roche Ltd and certain of its affiliates (collectively, Roche), Takeda Pharmaceutical Company Limited (Takeda), and Novartis Pharma AG and one of its affiliates (collectively, Novartis). Novartis owned approximately 13.3% of the Company's outstanding common stock as of December 31, 2009. The Company

Table of Contents**ALNYLAM PHARMACEUTICALS, INC.****NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

has also generated revenues from the National Institute of Allergy and Infectious Diseases ( NIAID ), a component of the National Institutes of Health ( NIH ), Cubist Pharmaceuticals, Inc. ( Cubist ), and the Defense Threat Reduction Agency ( DTRA ), an agency of the United States Department of Defense.

The following table summarizes customers with net revenues that represent greater than 10% of the Company's net revenues from research collaborators, for the periods indicated:

	<b>Year Ended December 31,</b>		
	<b>2009</b>	<b>2008</b>	<b>2007</b>
Roche	57%	57%	35%
Takeda	22%	13%	
Novartis	10%	12%	29%
NIAID			15%

The following table summarizes customers with amounts due that represent greater than 10% of the Company's collaboration receivables balance:

	<b>As of December 31,</b>	
	<b>2009</b>	<b>2008</b>
Novartis	40%	55%
Roche	27%	
NIAID	14%	22%
Cubist	11%	
DTRA		10%

***Fair Value Measurements***

Effective January 1, 2008, the Company adopted a newly issued accounting standard 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. 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 Company's adoption of this standard has had no impact on its operating results or financial position.

Effective January 1, 2009, the Company adopted a newly issued accounting standard for fair value measurements of all nonfinancial assets and nonfinancial liabilities not recognized or disclosed at fair value in the financial statements

on a recurring basis. The Company's adoption of this accounting standard for these nonfinancial assets and nonfinancial liabilities did not impact its consolidated financial statements, and the Company did not have any nonfinancial assets or nonfinancial liabilities that would be recognized or disclosed at fair value on a recurring basis as of December 31, 2009.

The following tables present information about the Company's assets that are measured at fair value on a recurring basis as of December 31, 2009 and 2008, and indicate 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 (adjusted), interest rates and yield curves. Fair values determined by Level 3 inputs utilize unobservable data points for the asset or liability, and include situations

**Table of Contents****ALNYLAM PHARMACEUTICALS, INC.****NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

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:

<b>Description</b>	<b>As of December 31, 2009</b>	<b>Quoted Prices in Active Markets (Level 1)</b>	<b>Significant Observable Inputs (Level 2)</b>	<b>Significant Unobservable Inputs (Level 3)</b>
Cash equivalents	\$ 129,113	\$ 129,113	\$	\$
Marketable securities (fixed income)				
Government obligations	185,087		185,087	
Corporate notes	89,220		89,220	
Commercial paper	12,994		12,994	
Municipal notes	8,700		8,700	
Marketable securities (equity holdings)	1,847		1,847	
Total	\$ 426,961	\$ 129,113	\$ 297,848	\$

<b>Description</b>	<b>As of December 31, 2008</b>	<b>Quoted Prices in Active Markets (Level 1)</b>	<b>Significant Observable Inputs (Level 2)</b>	<b>Significant Unobservable Inputs (Level 3)</b>
Cash equivalents	\$ 187,057	\$ 167,293	\$ 19,764	\$
Marketable securities (fixed income)				
Government obligations	196,000		196,000	
Corporate notes	68,136		68,136	
Commercial paper	56,133		56,133	
Marketable securities (equity holdings)	648		648	
Total	\$ 507,974	\$ 167,293	\$ 340,681	\$

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

***Investments in Marketable Securities***

The Company invests its excess cash balances in short-term and long-term marketable debt and equity securities. The Company classifies its investments in marketable debt securities as either held-to-maturity or available-for-sale based on facts and circumstances present at the time it purchased the securities. As of each balance sheet date presented, the Company classified all of its investments in debt and equity securities as available-for-sale. The Company reports available-for-sale investments at fair value as of each balance sheet date and includes any unrealized holding gains and losses (the adjustment to fair value) in stockholders' equity. Realized gains and losses are determined using the specific identification method and are included in investment income. If any adjustment to fair value reflects a decline in the value of the investment, the Company considers all available evidence to evaluate the extent to which the decline is other than temporary and, if so, marks the investment to market through a charge to its consolidated statements of operations. The Company did not record any impairment charges related to its fixed income marketable securities during the years ended December 31, 2009, 2008 or 2007. During 2008, the Company recorded an impairment charge of \$1.6 million related to its equity investment in Tekmira Pharmaceuticals Corporation ( Tekmira ), as the decrease in the fair value of this investment was deemed to be other than temporary. The Company's marketable securities are classified as cash equivalents if the original



**Table of Contents****ALNYLAM PHARMACEUTICALS, INC.****NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

maturity, from the date of purchase, is 90 days or less, and as marketable securities if the original maturity, from the date of purchase, is in excess of 90 days.

The following tables summarize the Company's marketable securities at December 31, 2009 and 2008, in thousands:

	<b>December 31, 2009</b>			
	<b>Amortized</b>	<b>Gross</b>	<b>Gross</b>	
	<b>Cost</b>	<b>Unrealized</b>	<b>Unrealized</b>	<b>Fair Value</b>
		<b>Gains</b>	<b>Losses</b>	
Municipal notes (Due within 1 year)	\$ 8,698	\$ 2	\$	\$ 8,700
Commercial paper (Due within 1 year)	12,991	3		12,994
Corporate notes (Due within 1 year)	36,976	52	(24)	37,004
Corporate notes (Due after 1 year through 2 years)	52,085	169	(38)	52,216
U.S. Government obligations (Due within 1 year)	85,061	205	(30)	85,236
U.S Government obligations (Due after 1 year through 2 years)	100,005	96	(250)	99,851
Equity securities	1,345	502		1,847
<b>Total</b>	<b>\$ 297,161</b>	<b>\$ 1,029</b>	<b>\$ (342)</b>	<b>\$ 297,848</b>

	<b>December 31, 2008</b>			
	<b>Amortized</b>	<b>Gross</b>	<b>Gross</b>	
	<b>Cost</b>	<b>Unrealized</b>	<b>Unrealized</b>	<b>Fair Value</b>
		<b>Gains</b>	<b>Losses</b>	
Commercial paper (Due within 1 year)	\$ 56,014	\$ 119	\$	\$ 56,133
Corporate notes (Due within 1 year)	37,504	262	(102)	37,664
Corporate notes (Due after 1 year through 2 years)	30,497	81	(106)	30,472
U.S. Government obligations (Due within 1 year)	143,872	927		144,799
U.S Government obligations (Due after 1 year through 2 years)	50,649	552		51,201
Equity securities	1,345		(697)	648
<b>Total</b>	<b>\$ 319,881</b>	<b>\$ 1,941</b>	<b>\$ (905)</b>	<b>\$ 320,917</b>

**Revenue Recognition**

The Company has entered into collaboration agreements with biotechnology and pharmaceutical companies, including Novartis, Biogen Idec Inc. ( Biogen Idec ), Roche, Takeda, Kyowa Hakko Kirin Co., Ltd. ( Kyowa Hakko Kirin ), Cubist

and Merck & Co., Inc. ( Merck ). The terms of the Company's collaboration agreements typically include non-refundable license fees, funding of research and development, payments based upon achievement of clinical and pre-clinical development milestones, manufacturing services and royalties on product sales.

Non-refundable license fees are recognized as revenue upon delivery of the license only if the Company has a contractual right to receive such payment, the contract price is fixed or determinable, the collection of the resulting receivable is reasonably assured and the Company has no further performance obligations under the license agreement. Multiple element arrangements, such as license and development arrangements, are analyzed to determine whether the deliverables, which often include a license and performance obligations such as research and steering committee services, can be separated or whether they must be accounted for as a single unit of accounting.

**Table of Contents**

**ALNYLAM PHARMACEUTICALS, INC.**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

The Company recognizes upfront license payments as revenue upon delivery of the license only if the license has stand-alone value and the fair value of the undelivered performance obligations, typically including research and/or steering committee services, can be determined. If the fair value of the undelivered performance obligations can be determined, such obligations are accounted for separately as such obligations are fulfilled. If the license is considered to either not have stand-alone value or have stand-alone value but the fair value of any of the undelivered performance obligations cannot be determined, the arrangement would then be accounted for as a single unit of accounting and the license payments and payments for performance obligations are recognized as revenue over the estimated period of when the performance obligations are performed.

Whenever the Company determines that an arrangement should be accounted for as a single unit of accounting, the Company determines the period over which the performance obligations will be performed and revenue will be recognized. Revenue will be recognized using either a proportional performance or straight-line method. The Company recognizes revenue using the proportional performance method when the level of effort required to complete its performance obligations under an arrangement can be reasonably estimated and such performance obligations are provided on a best-efforts basis. Direct labor hours or full-time equivalents are typically used as the measure of performance. Revenue recognized under the proportional performance method would be determined by multiplying the total payments under the contract, excluding royalties and payments contingent upon achievement of substantive milestones, by the ratio of level of effort incurred to date to estimated total level of effort required to complete the Company's performance obligations under the arrangement. Revenue is limited to the lesser of the cumulative amount of payments received or the cumulative amount of revenue earned, as determined using the proportional performance method, as of the period ending date.

If the level of effort to complete its performance obligations under an arrangement cannot be reasonably estimated, then revenue under the arrangement would be recognized as revenue on a straight-line basis over the period the Company is expected to complete its performance obligations. Revenue is limited to the lesser of the cumulative amount of payments received or the cumulative amount of revenue earned, as determined using the straight-line method, as of the period ending date.

Many of the Company's collaboration agreements entitle it to additional payments upon the achievement of performance-based milestones. If the achievement of a milestone is considered probable at the inception of the collaboration, the related milestone payment is included with other collaboration consideration, such as upfront fees and research funding, in the Company's revenue model. Milestones that involve substantial effort on the Company's part and the achievement of which are not considered probable at the inception of the collaboration are considered substantive milestones. Substantive milestones are included in the Company's revenue model when achievement of the milestone is considered probable. As future substantive milestones are achieved, a portion of the milestone payment, equal to the percentage of the performance period completed when the milestone is achieved, multiplied by the amount of the milestone payment, will be recognized as revenue upon achievement of such milestone. The remaining portion of the milestone will be recognized over the remaining performance period using the proportional performance or straight-line method. Milestones that are tied to regulatory approval are not considered probable of being achieved until such approval is received. Milestones tied to counter-party performance are not included in the Company's revenue model until the performance conditions are met.

Steering committee services that are not inconsequential or perfunctory and that are determined to be performance obligations are combined with other research services or performance obligations required under an arrangement, if

any, in determining the level of effort required in an arrangement and the period over which the Company expects to complete its aggregate performance obligations.

For revenue generating arrangements where the Company, as a vendor, provides consideration to a licensor or collaborator, as a customer, the Company applies the accounting standard that governs such transactions. This standard addresses the accounting for revenue arrangements where both the vendor and the customer make cash payments to each other for services and/or products. A payment to a customer is presumed to be a reduction of the selling price unless the Company receives an identifiable benefit for the payment and it can reasonably estimate the

**Table of Contents**

**ALNYLAM PHARMACEUTICALS, INC.**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

fair value of the benefit received. Payments to a customer that are deemed a reduction of selling price are recorded first as a reduction of revenue, to the extent of both cumulative revenue recorded to date and probable future revenues, which include any unamortized deferred revenue balances, under all arrangements with such customer, and then as an expense. Payments that are not deemed to be a reduction of selling price would be recorded as an expense.

The Company evaluates its collaborative agreements for proper classification in its consolidated statements of operations based on the nature of the underlying activity. Transactions between collaborators recorded in the Company's consolidated statements of operations are recorded on either a gross or net basis, depending on the characteristics of the collaborative relationship. The Company generally reflects amounts due under its collaborative agreements related to cost-sharing of development activities as a reduction of research and development expense.

Revenue under government cost reimbursement contracts is recognized as the Company performs the underlying research and development activities.

Amounts received prior to satisfying the above revenue recognition criteria are recorded as deferred revenue in the accompanying consolidated balance sheets. Amounts not expected to be recognized within the next 12 months are classified as long-term deferred revenue. As of December 31, 2009, the Company had short-term and long-term deferred revenue of \$81.9 million and \$189.9 million, respectively, related to its collaborations.

***Income Taxes***

The Company uses the asset and liability method of accounting for income taxes. Under the asset and liability method, deferred tax assets and liabilities reflect the impact of temporary differences between amounts of assets and liabilities for financial reporting purposes and such amounts as measured under enacted tax laws. A valuation allowance is required to offset any net deferred tax assets if, based upon the available evidence, it is more likely than not that some or all of the deferred tax asset will not be realized.

The Company accounts for uncertain tax positions using a more-likely-than-not threshold for recognizing and resolving uncertain tax positions. The evaluation of uncertain tax positions is based on factors that include, but are not limited to, changes in tax law, the measurement of tax positions taken or expected to be taken in tax returns, the effective settlement of matters subject to audit, new audit activity and changes in facts or circumstances related to a tax position.

***Research and Development Costs***

Research and development costs are expensed as incurred. Included in research and development costs are wages, benefits and other operating costs, facilities, supplies, external services, clinical trial and manufacturing costs and overhead directly related to the Company's research and development operations as well as costs to acquire technology licenses.

The Company has entered into several license agreements for rights to utilize certain technologies. The terms of the licenses may provide for upfront payments, annual maintenance payments, milestone payments based upon certain specified events being achieved and royalties on product sales. Costs to acquire and maintain licensed technology that has not reached technological feasibility and does not have alternative future use are charged to research and

development expense as incurred. During the years ended December 31, 2009, 2008 and 2007, the Company charged to research and development expense costs associated with license fees of \$13.6 million, \$12.6 million and \$42.2 million, respectively. License fees for 2007 were primarily the result of \$27.5 million in payments to certain entities, primarily Isis Pharmaceuticals, Inc. ( Isis ), in connection with the Roche alliance and \$14.7 million in charges for licenses for certain delivery technologies.

**Table of Contents**

**ALNYLAM PHARMACEUTICALS, INC.**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

***Estimated Liability for Development Costs***

The Company records accrued liabilities related to expenses for which service providers have not yet billed the Company with respect to products or services that the Company has received, specifically related to ongoing pre-clinical studies and clinical trials. These costs primarily relate to third-party clinical management costs, laboratory and analysis costs, toxicology studies and investigator fees. The Company has multiple product candidates in concurrent pre-clinical studies and clinical trials at multiple clinical sites throughout the world. In order to ensure that the Company has adequately provided for ongoing pre-clinical and clinical development costs during the period in which the Company incurs such costs, the Company maintains an accrual to cover these expenses. The Company updates the estimate for this accrual on at least a quarterly basis. The assessment of these costs is a subjective process that requires judgment. Upon settlement, these costs may differ materially from the amounts accrued in the Company's consolidated financial statements. The Company's historical accrual estimates have not been materially different from the Company's actual amounts.

***Accounting for Stock-Based Compensation***

Effective January 1, 2006, the Company adopted a newly issued accounting standard addressing recognition and disclosure of stock compensation. The Company adopted the fair value recognition provisions of this standard using the modified-prospective-transition method. The Company has stock option plans and an employee stock purchase plan under which it grants equity instruments that are required to be evaluated under this standard. For stock options granted to non-employees compensation expense is generally recognized over the vesting period of the award, which is generally the period during which services are rendered by such non-employees. At the end of each financial reporting period prior to vesting, the value of these options (as calculated using the Black-Scholes option-pricing model) is re-measured using the then-current fair value of the Company's common stock. Stock options granted by the Company to non-employees, other than members of the Company's Board of Directors and Scientific Advisory Board members, generally vest over a four-year service period. The Company accounts for non-employee grants as an expense over the vesting period of the underlying stock.

***Accounting for Joint Venture***

The Company accounts for its interest in Regulus using the equity method of accounting. The Company reviewed the consolidation guidance that defines a variable interest entity ( VIE ) and concluded that Regulus currently qualifies as a VIE. The founding investor rights agreement ( Investor Rights Agreement ) contains transfer restrictions on each of Isis and the Company's interests and, as a result, the Company and Isis are considered related parties. Because the Company and Isis are related parties and collectively own 100% of Regulus, the determination of which entity would be considered the primary beneficiary is based on which entity is most closely associated with Regulus. Following consolidation guidance, the Company has concluded that Isis is the primary beneficiary and, accordingly, the Company has not consolidated Regulus and accounts for its investment under the equity method of accounting. Under new consolidation guidance effective January 1, 2010, the Company does not expect Isis to continue to consolidate Regulus.

***Comprehensive Loss***

Comprehensive loss is comprised of net loss and certain changes in stockholders' equity that are excluded from net loss. The Company includes foreign currency translation adjustments in other comprehensive loss for Alnylam Europe as the functional currency is not the United States dollar. The Company also includes unrealized gains and losses on certain marketable securities in other comprehensive loss.

*Net Loss Per Common 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



**Table of Contents****ALNYLAM PHARMACEUTICALS, INC.****NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

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:

	<b>December 31,</b>		
	<b>2009</b>	<b>2008</b>	<b>2007</b>
Options to purchase common stock	7,927	7,037	5,304
Unvested restricted common stock		29	57
Options that were exercised before vesting			11
	7,927	7,066	5,372

***Segment Information***

The Company operates in a single reporting segment, the discovery, development and commercialization of RNAi therapeutics.

***Subsequent Events***

The Company evaluated all events or transactions that occurred after December 31, 2009 up through the date these consolidated financial statements were issued. During this period, the Company did not have any material recognizable or unrecognizable subsequent events.

***Recent Accounting Pronouncements***

In June 2009, the Financial Accounting Standards Board ( FASB ) issued the FASB Accounting Standards Codification ( ASC ). Effective in the third quarter of 2009, the ASC became the single source for all authoritative GAAP recognized by the FASB, and is required to be applied to financial statements issued for interim and annual periods ending after September 15, 2009. The ASC does not change GAAP and did not impact the Company's consolidated financial statements.

In October 2009, the FASB issued a new accounting standard, which amends existing revenue recognition accounting pronouncements and provides accounting principles and application guidance on whether multiple deliverables exist, how the arrangement should be separated, and the consideration allocated. This standard eliminates the requirement to establish the fair value of undelivered products and services and instead provides for separate revenue recognition

based upon management's estimate of the selling price for an undelivered item when there is no other means to determine the fair value of that undelivered item. Previously, accounting principles required that the fair value of the undelivered item be the price of the item either sold in a separate transaction between unrelated third parties or the price charged for each item when the item is sold separately by the vendor. This was difficult to determine when the product was not individually sold because of its unique features. If the fair value of all of the elements in the arrangement was not determinable, then revenue was deferred until all of the items were delivered or fair value was determined. This new approach is effective prospectively for revenue arrangements entered into or materially modified in fiscal years beginning on or after June 15, 2010. The Company is currently evaluating the potential impact of this accounting standard on its consolidated financial statements.

In June 2009, the FASB issued a new accounting standard, which has not yet been integrated into the ASC. Accordingly, it will remain authoritative until integrated. Statement of Financial Accounting Standards ( SFAS )

Table of Contents**ALNYLAM PHARMACEUTICALS, INC.****NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

No. 167, Amendments to FASB Interpretation No. 46(R) ( SFAS 167 ) amends previously issued accounting guidance for the consolidation of a VIE to require an enterprise to determine whether its variable interest or interests give it a controlling financial interest in a VIE. This amended consolidation guidance for VIEs also replaces the existing quantitative approach for identifying which enterprise should consolidate a VIE, which was based on which enterprise was exposed to a majority of the risks and rewards, with a qualitative approach, based on which enterprise has both (1) the power to direct the economically significant activities of the entity and (2) the obligation to absorb losses of the entity that could potentially be significant to the VIE or the right to receive benefits from the entity that could potentially be significant to the VIE. This new accounting standard has broad implications and may affect how the Company accounts for the consolidation of common structures, such as joint ventures, equity method investments, collaboration and other agreements, and purchase arrangements. Under this revised consolidation guidance, more entities may meet the definition of a VIE, and the determination about which entity should consolidate a VIE is required to be evaluated continuously. The Company has completed an evaluation of the impact of adopting this standard and determined that the adoption will not have an impact on its consolidated financial statements.

**3. SIGNIFICANT AGREEMENTS**

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

	<b>Year Ended December 31,</b>		
	<b>2009</b>	<b>2008</b>	<b>2007</b>
Roche	\$ 56,884	\$ 54,427	\$ 17,571
Takeda	21,732	12,794	
Novartis	9,811	11,635	14,670
Government contract	7,471	14,172	9,800
Cubist	2,672		
Biogen Idec	921	928	3,427
Merck			3,903
Other	1,042	2,207	1,526
<b>Total net revenues from research collaborators</b>	<b>\$ 100,533</b>	<b>\$ 96,163</b>	<b>\$ 50,897</b>

***Platform Alliances******Roche Alliance***

In July 2007, the Company and, for limited purposes, Alnylam Europe, entered into a License and Collaboration Agreement (the LCA) with Roche. Under the LCA, which became effective in August 2007, the Company granted Roche a non-exclusive license to the Company's intellectual property to develop and commercialize therapeutic products that function through RNAi, subject to the Company's existing contractual obligations to third parties. The license is initially limited to the therapeutic areas of oncology, respiratory diseases, metabolic diseases and certain

liver diseases, and may be expanded to include up to 18 additional therapeutic areas, comprising substantially all other fields of human disease, as identified and agreed upon by the parties, upon payment to the Company by Roche of an additional \$50.0 million for each additional therapeutic area, if any.

In consideration for the rights granted to Roche under the LCA, Roche paid the Company \$273.5 million in upfront cash payments. In addition, in exchange for the Company's contributions under the LCA, for each RNAi therapeutic product developed by Roche, its affiliates or sublicensees under the LCA, the Company is entitled to receive milestone payments upon achievement of specified development and sales events, totaling up to an

**Table of Contents**

**ALNYLAM PHARMACEUTICALS, INC.**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

aggregate of \$100.0 million per therapeutic target, together with royalty payments based on worldwide annual net sales, if any.

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. In October 2009, the Company and Roche advanced their alliance to initiate this therapeutic collaboration stage. Under this Discovery Collaboration, the Company and Roche are collaborating on the discovery and development of specific RNAi therapeutic products and each party contributes key delivery technologies in the effort, which is focused on specific disease targets. The Company and Roche intend to co-develop and co-commercialize RNAi therapeutic products in the U.S. market and the Company is eligible to receive additional milestone and royalty payments for products developed in the rest of the world, if any. After a pre-specified period of collaborative activities, each party will have the option to opt-out of the day-to-day development activities in exchange for reduced milestones and royalty payments in the future. The Discovery Collaboration is governed by the joint steering committee that is comprised of an equal number of representatives from each party.

The term of the LCA generally ends upon the later of ten years from the first commercial sale of a licensed product and the expiration of the last-to-expire patent covering a licensed product. Roche may terminate the LCA, on a licensed product-by-licensed product, licensed patent-by-licensed patent, and country-by-country basis, upon 180-days prior written notice, but is required to continue to make milestone and royalty payments to the Company if any royalties were payable on net sales of a terminated licensed product during the previous 12 months. The LCA may also be terminated by either party in the event the other party fails to cure a material breach under the LCA.

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.

Under the terms of the Common Stock Purchase Agreement, in the event the Company proposes to sell or issue any of its equity securities, subject to specified exceptions, it has agreed to grant to Roche Finance the right to acquire, at fair value, additional securities, such that Roche Finance would be able to maintain its ownership percentage in the Company.

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 ( 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) \$1.0 million and \$4.2 million for these services for the years ended December 31, 2008 and 2007, respectively.

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

**Table of Contents**

**ALNYLAM PHARMACEUTICALS, INC.**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

employees. The Company recorded \$3.8 million of stock-based compensation expense during 2007 related to the restricted share grants and the stock option modifications.

In summary, the Company received upfront payments totaling \$331.0 million under the Roche alliance, which include 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 initially recorded \$278.2 million of these proceeds as deferred revenue in connection with the Roche alliance. The Company allocated \$51.3 million and \$1.5 million for financial statement purposes related to the common stock issuance and the net book value of Alnylam Europe, respectively.

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 is obligated to perform under the Discovery Collaboration. The Company has determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, 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 in order to utilize a proportional performance model. As future substantive milestones are achieved, a portion of the milestone payment, equal to the percentage of the performance period completed when the milestone is achieved, multiplied by the amount of the milestone payment, will be recognized as revenue upon achievement of such milestone. The remaining portion of the milestone will be recognized over the remaining performance period on a straight-line basis.

In connection with the LCA and the Common Stock Purchase Agreement, during 2007, the Company paid \$27.5 million of license fees to the Company's licensors, primarily Isis, in accordance with the applicable license agreements with those parties. These fees were charged to research and development expense.

*Takeda Alliance*

In May 2008, the Company entered into a license and collaboration agreement (the Takeda Collaboration Agreement) with 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 an upfront payment of \$100.0 million. Takeda is also required to make the additional \$50.0 million in payments to the Company upon



**Table of Contents**

**ALNYLAM PHARMACEUTICALS, INC.**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

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 due upon achievement of specified technology transfer activities, but no later than May 2010, and \$10.0 million of which is due upon achievement of specified technology transfer activities within 24 to 36 months after 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, if any, comprising substantially all other fields of human disease, as identified and agreed upon by the parties. In addition, for each RNAi therapeutic product developed by Takeda, its affiliates and sublicensees, the Company is entitled to receive specified development and commercialization milestones, totaling up to \$171.0 million per product, together with royalty payments based on worldwide annual net sales, if any.

Pursuant to the Takeda Collaboration Agreement, the Company and Takeda are also collaborating 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-RSV 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.

The term of the Takeda Collaboration Agreement generally ends upon the later of (1) the expiration of the Company's last-to-expire patent covering a licensed product and (2) the last-to-expire term of a profit sharing agreement in the event the Company elects to enter into such an agreement. The Takeda Collaboration Agreement may be terminated by either party in the event the other party fails to cure a material breach under the agreement. In addition, Takeda may terminate the agreement on a licensed product-by-licensed product or country-by-country basis upon 180-days prior written notice to the Company, provided, however, that Takeda is required to continue to make royalty payments to the Company for the duration of the royalty term with respect to a licensed product.

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 the accounting guidance governing revenue recognition on multiple element arrangements, 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 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, the receipt of which the Company believes is probable, 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, in order to utilize a proportional performance model. As future substantive milestones are achieved, a portion of the milestone payment, equal to the percentage of the performance period completed when the milestone is achieved, multiplied by the amount of the milestone payment, will be recognized as revenue upon achievement of such milestone. The remaining portion of the milestone will be recognized over the remaining performance period on a straight-line basis.

**Table of Contents**

**ALNYLAM PHARMACEUTICALS, INC.**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

In connection with the Takeda Collaboration Agreement, during 2008, the Company paid \$5.0 million of license fees to the Company's licensors, primarily Isis, in accordance with the applicable license agreements with those parties. These fees were charged to research and development expense.

***Discovery and Development Alliances***

***Isis Collaboration and License Agreement***

In April 2009, the Company and Isis amended and restated their existing strategic collaboration and license agreement (as amended and restated, the Amended and Restated Isis Agreement), originally entered into in March 2004, to extend the broad cross-licensing arrangement regarding double-stranded RNAi that was established in 2004, pursuant to which Isis granted the Company licenses to its current and future patents and patent applications relating to chemistry and to RNA-targeting mechanisms for the research, development and commercialization of double-stranded RNA ( dsRNA ) products. The Company has the right to use Isis technologies in its development programs or in collaborations and Isis has agreed not to grant licenses under these patents to any other organization for the discovery, development or commercialization of dsRNA products designed to work through an RNAi mechanism, except in the context of a collaboration in which Isis plays an active role. The Company granted Isis non-exclusive licenses to its current and future patents and patent applications relating to RNA-targeting mechanisms and to chemistry for research use. The Company also granted Isis the non-exclusive right to develop and commercialize dsRNA products developed using RNAi technology against a limited number of targets. In addition, the Company granted Isis non-exclusive rights to research, develop and commercialize single-stranded RNA products.

Under the terms of the Isis agreement, the Company paid Isis an upfront license fee of \$5.0 million. The Company also agreed to pay Isis milestone payments, totaling up to approximately \$3.4 million, upon the occurrence of specified development and regulatory events, and royalties on sales, if any, for each product that the Company or a collaborator develops using Isis intellectual property. In addition, the Company agreed to pay to Isis a percentage of specified fees from strategic collaborations the Company may enter into that include access to the Isis intellectual property.

Isis agreed to pay the Company, per therapeutic target, a license fee of \$0.5 million, and milestone payments totaling approximately \$3.4 million, payable upon the occurrence of specified development and regulatory events, and royalties on sales, if any, for each product developed by Isis or a collaborator that utilizes the Company's intellectual property. Isis has the right to elect up to ten non-exclusive target licenses under the agreement and has the right to purchase one additional non-exclusive target per year during the term of the collaboration.

As part of the Amended and Restated Isis Agreement, the Company and Isis established a new collaborative effort focused on the development of single stranded RNAi ( ssRNAi ) technology. Under the Amended and Restated Isis Agreement, the Company obtained from Isis a co-exclusive, worldwide license to Isis' current and future patents and patent applications relating to chemistry and RNA-targeting mechanisms to research, develop and commercialize ssRNAi products. Each of the Company and Isis has the opportunity to discover and develop drugs employing the ssRNAi technology. Under the terms of the Amended and Restated Isis Agreement, the Company will potentially pay Isis up to an aggregate of \$31.0 million in license fees, payable in four tranches, that include \$11.0 million paid on signing, \$10.0 million payable in October 2010, or if and when *in vivo* efficacy in rodents is demonstrated if sooner, \$5.0 million upon achievement of *in vivo* efficacy in non-human primates, and \$5.0 million upon initiation of the first

clinical trial with an ssRNAi drug, subject to the Company's right to unilaterally terminate the research program. The Company is funding research activities at a minimum of \$3.0 million each year for three years with research and development activities conducted by both the Company and Isis. If the Company develops and commercializes drugs utilizing ssRNAi technology on its own or with a partner, the Company would be required to make milestone payments to Isis, totaling up to \$18.5 million per product, as well as royalties. Also, Isis initially is eligible to receive up to 50% of any sublicense payments due to the Company from a third party based on the Company's partnering of ssRNAi products, which

**Table of Contents**

**ALNYLAM PHARMACEUTICALS, INC.**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

amount will decline over time as the Company's investment in the technology and drugs increases. In turn, the Company is eligible to receive up to five percent of any sublicense payments due to Isis from a third party based on Isis' partnering of ssRNAi products.

The Company has the unilateral right to terminate the ssRNAi research program before September 30, 2010, in which event any licenses to ssRNAi products granted by Isis to the Company under the Amended and Restated Isis Agreement, and any obligation thereunder by the Company to pay milestone payments, royalties or sublicense payments to Isis for such ssRNAi products, would also terminate.

The term of the Amended and Restated Isis Agreement generally ends upon the expiration of the last-to-expire patent licensed thereunder, whether such patent is a patent licensed by the Company to Isis, or vice versa. As the license will include additional patents, if any, filed to cover future inventions, if any, the date of expiration cannot be determined at this time.

During 2009, as a result of certain payments received by the Company in connection with the Cubist alliance, the Company paid \$1.0 million to Isis. During 2008, as a result of certain payments received by the Company in connection with the Takeda alliance, the Company paid \$4.6 million to Isis. During 2007, as a result of certain payments received by the Company in connection with the Roche alliance, the Company paid \$26.5 million to Isis. These license fees were charged to research and development expense in the respective periods.

*Novartis Broad Alliance*

Beginning in September 2005, the Company entered into a series of transactions with 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") (collectively the "Novartis Agreements"). The Collaboration and License Agreement had an initial term of three years, with an option for two additional one-year extensions at the election of Novartis. In July 2009, Novartis elected to further extend the term for the fifth and final planned year, through October 2010.

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. In addition, under the Investor Rights Agreement, the Company granted Novartis rights to acquire additional equity securities in the event that the Company proposes to sell or issue any equity securities, subject to specified exceptions, as described in the Investor Rights Agreement, 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. In May 2009, Novartis purchased 65,922 shares of the Company's common stock at a purchase price of \$17.50 per share, resulting in an aggregate payment to the Company of \$1.2 million. This purchase allowed Novartis to maintain its ownership position of 13.4% of the Company's outstanding common stock. The exercises of this right did not result in any changes to existing rights or any additional rights to Novartis. Further, during the term described in the Investor Rights Agreement, Novartis is

permitted to own no more than 19.9% of the Company's outstanding shares. At December 31, 2009, Novartis owned 13.3% of the Company's outstanding common stock.

Under the terms of the Collaboration and License Agreement, the Company and Novartis are working together on a defined number of selected targets, as defined in the Collaboration and License Agreement, to discover and develop therapeutics based on RNAi. In consideration for the rights granted to Novartis under the Collaboration and License Agreement, Novartis made upfront payments totaling \$10.0 million to the Company in October 2005, partly to reimburse prior costs incurred by the Company to develop *in vivo* RNAi technology. The Collaboration and

**Table of Contents**

**ALNYLAM PHARMACEUTICALS, INC.**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

License Agreement also includes terms under which Novartis is providing the Company with research funding and development milestone payments, and may provide the Company in the future with sales milestone payments as well as royalties on annual net sales of products resulting from the Collaboration and License Agreement, if any. The amount of research funding provided by Novartis under the Collaboration and License Agreement during the research term is dependent upon the number of active programs on which the Company is collaborating with Novartis at any given time and the number of Company employees that are working on those programs, in respect of which Novartis reimburses the Company at an agreed upon rate. Under the terms of the Collaboration and License Agreement, Novartis has the right to select up to 30 exclusive targets to include in the collaboration, which number may be increased to 40 under certain circumstances and upon additional payments. For RNAi therapeutic products developed under the Collaboration and License Agreement, if any, the Company would be entitled to receive milestone payments upon achievement of certain specified development and annual net sales events, up to an aggregate of \$75.0 million per therapeutic product.

Under the terms of the Collaboration and License Agreement, the Company retains the right to discover, develop, commercialize and manufacture compounds that function through the mechanism of RNAi, or products that contain such compounds as an active ingredient, with respect to targets not selected by Novartis for inclusion in the collaboration, provided that Novartis has a right of first offer with respect to an exclusive license for additional targets before the Company partners any of those additional targets with third parties.

The Collaboration and License Agreement also provides Novartis with a non-exclusive option to integrate into its operations the Company's intellectual property relating to RNAi technology, excluding any technology related to delivery of nucleic acid based molecules (the Integration Option). Novartis may exercise this Integration Option at any point during the research term, which term is currently expected to expire in the fourth quarter of 2010. In connection with the exercise of the Integration Option, Novartis would be required to make additional payments to the Company totaling \$100.0 million, payable in full at the time of exercise, which payments would include an option exercise fee, a milestone based on the overall success of the collaboration, and pre-paid milestones and royalties that could become due as a result of future development of products using the Company's technology. This amount would be offset by any license fees due to the Company's licensors in accordance with the applicable license agreements with those parties. In addition, under this license grant, Novartis may be required to make milestone and royalty payments to the Company in connection with the development and commercialization of RNAi therapeutic products, if any. The license grant under the Integration Option, if exercised by Novartis, would be structured similarly to the Company's non-exclusive platform licenses with Roche and Takeda.

Novartis may terminate the Collaboration and License Agreement in the event that the Company materially breaches its obligations. The Company may terminate the Collaboration and License Agreement with respect to particular programs, products and/or countries in the event of specified material breaches by Novartis of its obligations, or in its entirety under specified circumstances for multiple such breaches.

The Company initially deferred the non-refundable \$10.0 million upfront payment and the \$6.4 million premium received that represented the difference between the purchase price and the closing price of the common stock of the Company on the date of the stock purchase from Novartis. These payments, in addition to research funding and certain milestone payments, the receipt of which is considered probable, together total \$64.8 million, and are being 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.

As future substantive milestones are achieved, and to the extent they are within the period of performance, milestone payments will be recognized as revenue on a proportional performance basis over the contract's entire performance period, starting with the contract's commencement. A portion of the milestone payment, equal to the percentage of total performance completed when the milestone is achieved, multiplied by the milestone payment,



**Table of Contents**

**ALNYLAM PHARMACEUTICALS, INC.**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

will be recognized as revenue upon achievement of the milestone. The remaining portion of the milestone will be recognized over the remaining performance period under the proportional performance method.

The Company believes the estimated period of performance under the Collaboration and License Agreement is ten years, which includes the three-year initial term of the agreement, two one-year extensions elected by Novartis and limited support as part of a technology transfer until 2015, the fifth anniversary of the termination of the Collaboration and License Agreement. The Company continues to use an expected term of ten years in its proportional performance model. The Company reevaluates 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.

*Novartis Pandemic Flu Alliance*

In February 2006, the Company entered into an alliance with Novartis for the development of RNAi therapeutics for pandemic flu ( Novartis Flu Agreement ). Under the terms of the Novartis Flu Agreement, the Company and Novartis had joint responsibility for development of RNAi therapeutics for pandemic flu. This program was stopped during 2008 and currently there are no specific resource commitments for this program.

*Biogen Idec Collaboration Agreement*

In September 2006, the Company entered into a Collaboration and License Agreement (the Biogen Idec Collaboration Agreement ) with Biogen Idec focused on the discovery and development of therapeutics based on RNAi for the potential treatment of progressive multifocal leukoencephalopathy ( PML ). Under the terms of the Biogen Idec Collaboration Agreement, the Company granted Biogen Idec an exclusive license to distribute, market and sell certain RNAi therapeutics to treat PML and Biogen Idec has agreed to fund all related research and development activities. The Company received an upfront \$5.0 million payment from Biogen Idec. In addition, upon the successful development and utilization of a product resulting from the collaboration, if any, Biogen Idec would be required to pay the Company milestone payments, totaling \$51.0 million, and royalty payments on sales, if any.

The Company is recognizing revenue under the Biogen Idec collaboration on a straight-line basis over five years because the Company cannot reasonably estimate the total level of effort required to fulfill its obligations under this collaboration. The pace and scope of future development of this program is the responsibility of Biogen Idec.

Unless earlier terminated, the Biogen Idec Collaboration Agreement will remain in effect until the expiration of all payment obligations under the agreement. Either the Company or Biogen Idec may terminate the agreement in the event that the other party breaches its obligations thereunder. Biogen Idec may also terminate the agreement, on a country-by-country basis, without cause upon 90-days prior written notice.

*Merck Agreement*

In July 2006, the Company executed an Amended and Restated Research Collaboration and License Agreement (the Amended License Agreement ) with Merck. In September 2007, the Company and Merck terminated the Amended License Agreement (the Termination Agreement ). Pursuant to the Termination Agreement, all license grants of intellectual property to develop, manufacture and/or commercialize RNAi therapeutic products under the Amended

License Agreement ceased as of the date of the Termination Agreement, subject to certain specified exceptions. The Termination Agreement further provides that, subject to certain conditions, the Company and Merck will each retain sole ownership and rights in their own intellectual property. The Company has no remaining deliverables under the Amended License Agreement. The Company was recognizing the remaining deferred revenue of \$3.5 million under the Amended License Agreement, related to upfront cash payments and additional license fee payments received from Merck, on a straight-line basis over the

**Table of Contents**

**ALNYLAM PHARMACEUTICALS, INC.**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

remaining period of expected performance of four years. As a result of the Termination Agreement, the Company recognized this remaining deferred revenue of \$3.5 million during 2007.

***Product Alliances***

***Kyowa Hakko Kirin Alliance***

In June 2008, the Company entered into a License and Collaboration Agreement (the *Kyowa Hakko Kirin Agreement*) with Kyowa Hakko Kirin. Under the *Kyowa Hakko Kirin Agreement*, the Company granted Kyowa Hakko Kirin an exclusive license to its intellectual property in Japan and other markets in Asia (the *Licensed Territory*) for the development and commercialization of an RNAi therapeutic for the treatment of respiratory syncytial virus (RSV) infection. The *Kyowa Hakko Kirin Agreement* covers ALN-RSV01, as well as additional RSV-specific RNAi therapeutic compounds that comprise the ALN-RSV program (*Additional Compounds*). The Company retains all development and commercialization rights worldwide outside of the *Licensed Territory*, subject to our agreement with Cubist, described below.

Under the terms of the *Kyowa Hakko Kirin Agreement*, in June 2008, Kyowa Hakko Kirin paid the Company an upfront cash payment of \$15.0 million. In addition, Kyowa Hakko Kirin is required to make payments to the Company upon achievement of specified development and sales milestones totaling up to \$78.0 million, and royalty payments based on annual net sales, if any, of RNAi therapeutics for RSV by Kyowa Hakko Kirin, its affiliates and sublicensees in the licensed territory.

The collaboration between Kyowa Hakko Kirin 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 Kirin is establishing a development plan for the ALN-RSV program relating to the development activities to be undertaken in the *Licensed Territory*, with the initial focus on Japan. Kyowa Hakko Kirin is responsible, at its expense, for all development activities under the development plan that are reasonably necessary for the regulatory approval and commercialization of an RNAi therapeutic for the treatment of RSV in Japan and the rest of the *Licensed Territory*. The Company is responsible for supply of the product to Kyowa Hakko Kirin under a supply agreement unless Kyowa Hakko Kirin 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 term of the *Kyowa Hakko Kirin agreement* generally ends on a country-by-country basis upon the later of (1) the expiration of the Company's last-to-expire patent covering a licensed product and (2) the tenth anniversary of the first commercial sale in the country of sale. Additional patent filings relating to the collaboration may be made in the future. The *Kyowa Hakko Kirin 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 Kirin may terminate the agreement without cause upon 180-days' prior written notice to the Company, subject to certain conditions.

The Company has determined that the deliverables under the *Kyowa Hakko Kirin Agreement* include the license, the joint steering committee, the manufacturing services and any *Additional Compounds*. The Company has determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, 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 Kirin Agreement, as it is unable to estimate the timeline of its deliverables related to the fixed-price option granted to Kyowa Hakko Kirin for any Additional Compounds. The Company is deferring all revenue under the Kyowa Hakko Kirin 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 Kirin Agreement.

**Table of Contents****ALNYLAM PHARMACEUTICALS, INC.****NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)***Cubist Alliance*

In January 2009, the Company entered into a license and collaboration agreement with Cubist (the *Cubist Agreement*) to develop and commercialize therapeutic products ( *Licensed Products* ) based on certain of the Company's RNAi technology for the treatment of RSV infection. Licensed Products initially included ALN-RSV01, as well as several other second-generation RNAi-based RSV inhibitors. In November 2009, the Company and Cubist entered into an amendment to the *Cubist Agreement* (the *Amendment* ), which provides that the Company and Cubist will focus their collaboration and joint development efforts on ALN-RSV02, a second-generation compound, intended for use in pediatric patients. Consistent with the original *Cubist Agreement*, the Company and Cubist each bears one-half of the related development costs for ALN-RSV02. Pursuant to the terms of the *Amendment*, the Company is also continuing to develop ALN-RSV01 for adult transplant patients at its sole discretion and expense. Cubist has the right to resume the collaboration on ALN-RSV01 in the future, which right may be exercised for a specified period of time following the completion of the Company's Phase IIb trial of ALN-RSV01 in adult lung transplant patients infected with RSV, subject to the payment by Cubist of an opt-in fee representing reimbursement of an agreed upon percentage of certain of the Company's development expenses for ALN-RSV01.

Under the terms of the *Cubist Agreement*, the Company and Cubist share responsibility for developing *Licensed Products* in North America and each bears one-half of the related development costs, subject to the terms of the *Amendment*. The Company's collaboration with Cubist for the development of *Licensed Products* in North America is governed by a joint steering committee comprised of an equal number of representatives from each party. Cubist will have the sole right to commercialize *Licensed Products* in North America with costs associated with such activities and any resulting profits or losses to be split equally between the Company and Cubist. Throughout the rest of the world (the *Royalty Territory* ), excluding Asia, where the Company has previously partnered its ALN-RSV program with Kyowa Hakko Kirin, Cubist has an exclusive, royalty-bearing license to develop and commercialize *Licensed Products*.

In consideration for the rights granted to Cubist under the *Cubist Agreement*, in January 2009, Cubist made a \$20.0 million upfront cash payment to the Company. Cubist also has an obligation under the *Cubist Agreement* to pay the Company milestone payments, totaling up to an aggregate of \$82.5 million, upon the achievement of specified development and sales events in the *Royalty Territory*. In addition, if *Licensed Products* are successfully developed, Cubist will be required to pay to the Company royalties on net sales of *Licensed Products* in the *Royalty Territory*, if any, subject to offsets under certain circumstances. Upon achievement of certain development milestones, the Company will have the right to convert the North American co-development and profit sharing arrangement into a royalty-bearing license and, in addition to royalties on net sales in North America, will be entitled to receive additional milestone payments totaling up to an aggregate of \$130.0 million upon achievement of specified development and sales events in North America, subject to the timing of the conversion by the Company and the regulatory status of *Licensed Products* at the time of conversion. If the Company makes the conversion to a royalty-bearing license with respect to North America, then North America becomes part of the *Royalty Territory*.

During the term of the *Cubist Agreement*, neither party nor its affiliates may develop, manufacture or commercialize anywhere in the world, outside of Asia, a therapeutic or prophylactic product that specifically targets RSV, except for *Licensed Products* developed, manufactured or commercialized pursuant to the *Cubist Agreement*.

Unless terminated earlier in accordance with the agreement, the agreement expires on a country-by-country and licensed product-by-licensed product basis, (a) with respect to the Royalty Territory, upon the latest to occur of (1) the expiration of the last-to-expire Company patent covering a Licensed Product, (2) the expiration of the Regulatory-Based Exclusivity Period (as defined in the Cubist Agreement) and (3) ten years from first commercial sale in such country of such licensed product by Cubist or its affiliates or sublicensees, and (b) with respect to North America, if the Company has not converted North America into the Royalty Territory, upon the termination of the agreement by Cubist upon specified prior written notice. The Company estimates that its fundamental RNAi patents covered under the Cubist agreement will expire both in and outside of the United States generally between 2016 and

**Table of Contents**

**ALNYLAM PHARMACEUTICALS, INC.**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

2025. Certain claims covering ALN-RSV compounds in the United States would expire in 2026. These patent rights are subject to any potential patent term extensions and/or supplemental protection certificates extending such term extensions in countries where such extensions may become available. In addition, more patent filings relating to the collaboration may be made in the future. Cubist has the right to terminate the Cubist Agreement at any time (1) upon three months prior written notice if such notice is given prior to the acceptance for filing of the first application for regulatory approval of a Licensed Product or (2) upon nine months prior written notice if such notice is given after the acceptance for filing of the first application for regulatory approval. Either party may terminate the Cubist Agreement in the event the other party fails to cure a material breach or upon patent-related challenges by the other party.

The Company has determined that the deliverables under the Cubist Agreement include the licenses, technology transfer related to the ALN-RSV program, the joint steering committee and the development and manufacturing services that the Company is obligated to perform during the development period. The Company has determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the licenses and undelivered services are not separable and, accordingly, the licenses 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 Cubist Agreement, the last element to be delivered is the development and manufacturing services, which have an expected life of approximately eight years.

The Company is recognizing the upfront payment of \$20.0 million on a straight-line basis over approximately eight years because the Company is unable to reasonably estimate the level of effort to fulfill its performance obligations in order to utilize a proportional performance model. As future substantive milestones are achieved, a portion of the milestone payment, equal to the percentage of the performance period completed when the milestone is achieved, multiplied by the amount of the milestone payment, will be recognized as revenue upon achievement of such milestone. The remaining portion of the milestone will be recognized over the remaining performance period on a straight-line basis.

Under the terms of the Cubist Agreement, the Company and Cubist share responsibility for developing Licensed Products in North America and each bears one-half of the related development costs, provided that under the terms of the Amendment, the Company is funding the advancement of ALN-RSV01 for adult lung transplant patients and Cubist retains an opt-in right. For revenue generating arrangements that involve cost sharing between the parties, the Company presents the results of activities for which it acts as the principal on a gross basis and reports any payments received from (made to) other collaborators based on other applicable GAAP or, in the absence of other applicable GAAP, analogy to authoritative accounting literature or a reasonable, rational and consistently applied accounting policy election. As the Company is not considered the principal under the Cubist Agreement, the Company records any amounts due from Cubist as a reduction of research and development expense. For the year ended December 31, 2009, the Company and Cubist incurred \$11.4 million under the Cubist Agreement, of which \$11.0 million was incurred by the Company. During the year ended December 31, 2009, amounts due from Cubist of \$5.3 million were recorded as a reduction to research and development expense. As such, the Company recorded net research and development expenses of \$5.7 million in its consolidated statements of operations for the year ended December 31, 2009.

In connection with the Cubist Agreement, during 2009, the Company paid \$1.0 million of license fees to the Company's licensors, primarily Isis, in accordance with the applicable license agreements with those parties. These fees were charged to research and development expense.





**Table of Contents**

**ALNYLAM PHARMACEUTICALS, INC.**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

***Government Funding***

*NIH Contract*

In September 2006, NIAID awarded the Company 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. As a result of the continued progress of this program, the NIAID has appropriated the entire \$23.0 million over the four-year term of the contract, which will be completed in September 2010. The Company recognizes revenue under government cost reimbursement contracts as it performs the underlying research and development activities. At December 31, 2009, there was \$3.7 million of remaining funds available under the NIAID contract.

*Department of Defense Contract*

In August 2007, DTRA awarded the Company a contract to advance the development of a broad spectrum RNAi anti-viral therapeutic for hemorrhagic fever virus. The government initially committed to pay the Company up to \$10.9 million through February 2009, which included a six-month extension granted by DTRA in July 2008. Following a program review in early 2009, the Company and DTRA determined not to continue this program and accordingly, the remaining funds of up to \$27.7 million were not accessed. The Company recognizes revenue under government cost reimbursement contracts as it performs the underlying research and development activities.

***Delivery Technology***

The Company is working internally and with third-party collaborators 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 for the discovery, development and commercialization of lipid 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 consolidated balance sheets. During the year ended December 31, 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.

**Table of Contents****ALNYLAM PHARMACEUTICALS, INC.****NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)****4. INTANGIBLE ASSETS**

Intangible assets at December 31, 2009 and 2008 are as follows, in thousands:

	<b>December 31,</b>	
	<b>2009</b>	<b>2008</b>
Core technology	\$ 2,410	\$ 2,410
Less: accumulated amortization:	(1,788)	(1,615)
	<b>\$ 622</b>	<b>\$ 795</b>

During the years ended December 31, 2009, 2008 and 2007, the Company recorded \$0.2 million, \$0.2 million and \$0.3 million, respectively, of amortization expense related to core technology and workforce intangibles acquired from its acquisition of Ribopharma AG in 2003, of which the entire amount is included in research and development expenses. Workforce intangibles were fully amortized during 2007. Core technology is being amortized over its estimated useful life of ten years through 2013. The Company expects annual amortization expense related to the core technology intangible asset to be \$0.2 million through 2012 and \$0.1 million in 2013.

**5. PROPERTY AND EQUIPMENT**

Property and equipment consist of the following at December 31, 2009 and 2008, in thousands:

	<b>Useful Life</b>	<b>December 31,</b>	
		<b>2009</b>	<b>2008</b>
Laboratory equipment	5 years	\$ 16,126	\$ 12,617
Computer equipment and software	3 years	3,193	2,653
Furniture and fixtures	5 years	1,730	1,532
Leasehold improvements	*	18,851	18,126
Construction in progress			23
		39,900	34,951
Less: accumulated depreciation		(21,576)	(15,757)
		<b>\$ 18,324</b>	<b>\$ 19,194</b>

\* shorter of asset life or lease term

During the years ended December 31, 2009, 2008 and 2007, the Company recorded \$5.8 million, \$5.4 million and \$3.8 million, respectively, of depreciation expense related to its property and equipment.

## 6. NOTES PAYABLE

### *Equipment Lines of Credit*

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. 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%. In December 2008, the Company repaid the outstanding balance of \$1.7 million under the Oxford line of credit.

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

**Table of Contents****ALNYLAM PHARMACEUTICALS, INC.****NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

the agreement to allow the Company the ability to draw down amounts under the line of credit through December 31, 2005 upon adherence to certain conditions. Interest on the outstanding principal balance accrued at fixed rates of 9.25% to 10.25%. On the maturity of each equipment advance under the line of credit, the Company was required to pay, in addition to the principal and interest due, an additional amount of 11.5% of the original principal. This amount was accrued over the applicable borrowing period as additional interest expense. In December 2008, the Company repaid the outstanding balance of \$2.2 million under the Lighthouse line of credit.

At December 31, 2009 and 2008, the Company had no outstanding debt.

**7. COMMITMENTS AND CONTINGENCIES*****Manufacturing Commitment***

In January 2009, the Company and Tekmira entered into a manufacturing and supply agreement (the Tekmira Supply Agreement ) under which the Company committed to pay Tekmira a minimum of CAD\$11.2 million (representing U.S.\$9.2 million at the time of execution) over a three-year period beginning in January 2009. As of December 31, 2009, there was CAD\$6.3 million (representing U.S.\$6.0 million at December 31, 2009) of outstanding obligations under the Tekmira Supply Agreement, CAD\$3.5 million (representing U.S.\$3.3 million at December 31, 2009) of which the Company will pay in 2010 and CAD\$2.8 million (representing U.S.\$2.7 million at December 31, 2009) of which the Company will pay in 2011.

***Purchase Commitments***

The Company has future purchase commitments totaling \$10.1 million at December 31, 2009. These commitments are related to purchase orders, clinical and pre-clinical agreements, and other purchase commitments for goods or services. The Company has commitments of \$9.0 million, \$0.9 million and \$0.2 million in 2010, 2011 and 2012, respectively.

***Technology License Commitments***

The Company has licensed from third parties the rights to use certain technologies in its research process as well as in any products the Company may develop including these licensed technologies. In accordance with the related license agreements, the Company is required to make certain fixed payments to the licensor or a designee of the licensor over various agreement terms. Many of these agreement terms are consistent with the remaining lives of the underlying intellectual property that the Company has licensed. At December 31, 2009, the Company was committed to make the following fixed, cancellable payments under existing license agreements, in thousands:

**Year Ending December 31,**

2010	\$ 18,225(1)
2011	4,585
2012	1,973
2013	498

2014	543
Thereafter	6,823
Total	\$ 32,647

- (1) Includes a potential \$10.0 million milestone payable to Isis related to the continuation of the Company's ssRNAi collaboration. The Company has the unilateral right to terminate the portions of the Amended and Restated Isis Agreement related to ssRNAi before September 30, 2010, in which event any licenses to ssRNAi products granted by Isis to the Company under the Amended and Restated Isis Agreement, and any obligation

**Table of Contents****ALNYLAM PHARMACEUTICALS, INC.****NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

thereunder by the Company to pay milestone payments to Isis for such ssRNAi products, would also terminate. The remainder of the Amended and Restated Isis Agreement would remain in full force and effect.

***Operating Lease***

The Company leases office and laboratory space in Cambridge, Massachusetts for its corporate headquarters under a non-cancelable operating lease agreement. The Company also had a lease in Kulmbach, Germany through August 2007. Total rent expense, including operating expenses, under these operating leases was \$5.1 million, \$4.6 million and \$4.7 million for the years ended December 31, 2009, 2008 and 2007, respectively.

In 2003, the Company entered into an operating lease to rent laboratory and office space in Cambridge, Massachusetts (the Premises ) through September 2011. In March 2006, the Company amended its lease agreement to rent additional space at the Premises. Pursuant to the terms of the lease agreement, the Company secured a \$2.3 million letter of credit as security for the Premises.

In October 2007, the Company subleased from Archemix Corp. ( Archemix ) additional office and laboratory space at the Premises (the Sublease ). In connection with the execution of the Sublease, the Company issued a letter of credit in favor of Archemix in the amount of \$0.8 million.

In June 2009, the Company entered into an agreement with its landlord further amending provisions of its 2003 lease (the Amendment ). The Amendment provides for the lease of the entire second floor of the Premises, including space previously subleased by the Company from Archemix under the Sublease. Following execution of the Amendment, the Company leases and occupies approximately 95,000 square feet of office and laboratory space at the Premises under the lease, as amended. The term of the lease was extended an additional five years and now expires in September 2016. The Company has the option to extend the lease for two successive five-year extensions.

In connection with the execution of the Amendment and the concurrent termination of the Sublease, the landlord and Archemix released to the Company an aggregate of \$3.2 million being held under letters of credit as security deposits for the lease and the Sublease. This balance was previously classified as long-term restricted cash in the Company's consolidated balance sheet and was reclassified to cash and cash equivalents in 2009.

The Company received \$7.3 million in leasehold improvement incentives from its landlords in connection with its leases. These leasehold improvement incentives are being accounted for as a reduction in rent expense ratably over the lease term. The balance from these leasehold improvement incentives is included in current portion of deferred rent and deferred rent, net of current portion in the consolidated balance sheets at December 31, 2009 and 2008.

Future minimum payments under this non-cancelable lease are approximately as follows, in thousands:

**Year Ending December 31,**

2010	\$ 3,727
2011	3,773
2012	3,952

2013	4,110
2014	4,275
Thereafter	7,878
Total	\$ 27,715

***Litigation***

In June 2009, the Company joined with Max-Planck-Gesellschaft Zur Forderung Der Wissenschaften E.V. and Max-Planck-Innovation GmbH (collectively, "Max Planck"), in taking legal action against the Whitehead Institute for Biomedical Research ("Whitehead"), the Massachusetts Institute of Technology ("MIT") and the Board of



**Table of Contents**

**ALNYLAM PHARMACEUTICALS, INC.**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

Trustees of the University of Massachusetts ( UMass ). The complaint, initially filed in Suffolk County Superior Court in Boston, Massachusetts and subsequently removed to the U.S. District Court for the District of Massachusetts, alleges, among other things, that the defendants have improperly prosecuted the Tuschl I patent applications and wrongfully incorporated inventions covered by the Tuschl II patent applications into the Tuschl I patent applications, thereby potentially damaging the value of inventions reflected in the Tuschl I and Tuschl II patent applications. In the field of RNAi therapeutics, the Company is the exclusive licensee of the Tuschl I patent applications from Max Planck, MIT and Whitehead, and of the Tuschl II patent applications from Max Planck.

The complaint seeks to enjoin the defendants from taking any further action in connection with the prosecution of any Tuschl I application, a declaratory judgment and unspecified monetary damages. In August 2009, the court denied the Company's motion for a preliminary injunction. In addition, in August 2009, Whitehead and UMass filed counterclaims against the Company and Max Planck, including for breach of contract. A trial on the merits was originally scheduled to begin in February 2010. In January 2010, the Company and Max Planck filed a motion for leave to file an amended complaint expanding upon the allegations in the original complaint. In January 2010, the court granted this motion allowing the amended complaint and postponed the start of the trial. The Company currently expects the trial to start in June 2010.

In addition, in September 2009, the U.S. Patent and Trademark Office ( USPTO ), granted Max Planck's petition to revoke power of attorney in connection with the prosecution of the Tuschl I patent application. This action prevents the defendants from filing any papers with the USPTO in connection with further prosecution of the Tuschl I patent application without the agreement of Max Planck. Whitehead's petition to overturn the ruling on Max Planck's petition was denied.

Although the Company, along with Max Planck, are vigorously asserting their rights in this case, litigation is subject to inherent uncertainty and a court could ultimately rule against the Company and Max Planck. In addition, litigation is costly and may divert the attention of the Company's management and other resources that would otherwise be engaged in running the Company's business. The Company has not recorded an estimated liability associated with the legal proceedings described above due to the uncertainties related to both the likelihood and the amount of any potential loss.

***Indemnifications***

***Licensor indemnification*** In connection with the Company's license agreements with Max Planck relating to the Tuschl I and Tuschl II patent applications, the Company is required to indemnify Max Planck for certain damages arising in connection with the intellectual property rights licensed under the agreements. Under the Max Planck indemnification agreement, the Company is responsible for paying the costs of any litigation relating to the license agreements or the underlying intellectual property rights, including the costs associated with the litigation described above. These costs are charged to general and administrative expense. The Company believes that the probability of receiving a claim for damages is remote and, as such, no amounts have been accrued related to this indemnification at December 31, 2009 and 2008.

The Company is also a party to a number of agreements entered into in the ordinary course of business, which contain typical provisions that obligate the Company to indemnify the other parties to such agreements upon the occurrence of certain events. Such indemnification obligations are usually in effect from the date of execution of the applicable

agreement for a period equal to the applicable statute of limitations.

The maximum potential future liability of the Company under any such indemnification provisions is uncertain. The Company has determined that the estimated aggregate fair value of its potential liabilities under all such indemnification provisions is minimal and has not recorded any liability related to such indemnification provisions at December 31, 2009 or 2008.

**Table of Contents****ALNYLAM PHARMACEUTICALS, INC.****NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)****8. STOCKHOLDERS EQUITY*****Preferred Stock***

The Company has authorized up to 5,000,000 shares of preferred stock, \$0.01 par value per share, for issuance. The preferred stock will have such rights, preferences, privileges and restrictions, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences, as shall be determined by the Company's Board of Directors upon its issuance. At December 31, 2009 and 2008, there were no shares of preferred stock outstanding.

***Stockholder Rights Agreement***

On July 13, 2005, the Board of Directors of the Company declared a dividend of one right (collectively, the Rights) to buy one one-thousandth of a share of newly designated Series A Junior Participating Preferred Stock (Series A Junior Preferred Stock) for each outstanding share of the Company's common stock to stockholders of record at the close of business on July 26, 2005. Initially, the Rights are not exercisable and will be attached to all certificates representing outstanding shares of common stock, and no separate Rights Certificates will be distributed. The Rights will expire at the close of business on July 13, 2015 unless earlier redeemed or exchanged. Until a Right is exercised, the holder thereof, as such, will have no rights as a stockholder of the Company, including the right to vote or to receive dividends. Subject to the terms and conditions of the Rights Agreement entered into by the Company with Computershare (formerly EquiServe Trust Company, N.A.), as Rights Agent (the Rights Agreement), the Rights will become exercisable upon the earlier of (1) ten business days following the later of (a) the first date of a public announcement that a person or group (an Acquiring Person) acquires, or obtained the right to acquire, beneficial ownership of 20 percent or more of the outstanding shares of common stock of the Company or (b) the first date on which an executive officer of the Company has actual knowledge that an Acquiring Person has become such or (2) ten business days following the commencement of a tender offer or exchange offer that would result in a person or group beneficially owning more than 20 percent of the outstanding shares of common stock of the Company. Each Right entitles the holder to purchase one one-thousandth of a share of Series A Junior Preferred Stock at an initial purchase price of \$80.00 in cash, subject to adjustment. In the event that any person or group becomes an Acquiring Person, unless the event causing the 20% threshold to be crossed is a Permitted Offer (as defined in the Rights Agreement), each Right not owned by the Acquiring Person will entitle its holder to receive, upon exercise, that number of shares of common stock of the Company (or in certain circumstances, cash, property or other securities of the Company) which equals the exercise price of the Right divided by 50% of the current market price (as defined in the Rights Agreement) per share of such common stock at the date of the occurrence of the event. In the event that, at any time after any person or group becomes an Acquiring Person, (i) the Company is consolidated with, or merged with and into, another entity and the Company is not the surviving entity of such consolidation or merger (other than a consolidation or merger which follows a Permitted Offer) or if the Company is the surviving entity, but shares of its outstanding common stock are changed or exchanged for stock or securities (of any other person) or cash or any other property, or (ii) more than 50% of the Company's assets or earning power is sold or transferred, each holder of a Right (except Rights which previously have been voided as set forth in the Rights Agreement) shall thereafter have the right to receive, upon exercise, that number of shares of common stock of the acquiring company which equals the exercise price of the Right divided by 50% of the current market price of such common stock at the date of the occurrence of the event.

## 9. STOCK INCENTIVE PLANS

### *Stock Plans*

In June 2009, the Company's stockholders approved an amendment and restatement of the Company's 2004 Stock Incentive Plan (the Amended and Restated 2004 Plan), which replaced the Company's 2004 Stock Incentive Plan, as amended (the 2004 Plan). As of December 31, 2009, the Amended and Restated 2004 Plan provides for the granting of stock options to purchase up to 12,366,485 shares of common stock. Prior to the

**Table of Contents**

**ALNYLAM PHARMACEUTICALS, INC.**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

adoption of the Amended and Restated 2004 Plan, the Company was authorized to grant both options and restricted stock awards under the 2004 Plan. As of the effective date of the Amended and Restated 2004 Plan, the Company may only grant options under the Amended and Restated 2004 Plan, provided that the terms and conditions of any restricted stock awards outstanding under the 2004 Plan will continue to be governed by the Amended and Restated 2004 Plan.

In June 2009, the Company's stockholders also approved the Company's 2009 Stock Incentive Plan (the 2009 Plan). The 2009 Plan provides for the granting of stock options, restricted stock awards and units, stock appreciation rights and other stock-based awards to purchase up to 2,200,000 shares of common stock. The 2009 Plan has a fungible share pool. Any award that is not a full value award shall be counted against the authorized share limits specified in the 2009 Plan as one share for each share of common stock subject to award, and all full value awards, defined in the 2009 Plan as restricted stock awards or other stock-based awards, shall be counted as one and a half shares for each one share of common stock subject to such full value award. In addition, the 2009 Plan includes a non-employee director stock option program under which each eligible non-employee director is entitled to (1) a grant of an option to purchase 30,000 shares of common stock upon his or her initial appointment to the Board of Directors, or such other amount as the Board of Directors deems appropriate, and (2) a subsequent annual grant of an option to purchase 15,000 shares of common stock based on continued service, made on the date of each annual meeting of stockholders, provided the non-employee director has served as a director for at least six months and is serving as a director immediately prior to and following such annual meeting. The chairman of the audit committee will receive an additional annual grant of an option to purchase 10,000 shares of common stock based on continued service. Stock options granted by the Company to non-employee directors upon their appointment to the Board of Directors vest as to one-third of such shares on each of the first, second and third anniversaries of the date of grant, and at each year's annual meeting at which they serve as a director vest in full on the first anniversary of the date of grant.

At December 31, 2009, an aggregate of 11,555,081 shares of common stock were reserved for issuance under the Company's stock plans, including outstanding options to purchase 7,926,653 shares of common stock and 3,628,428 shares available for future grant under the Company's stock plans. Each option shall expire within ten years of issuance. Stock options granted by the Company to employees generally vest as to 25% of the shares on the first anniversary of the grant date and 6.25% of the shares at the end of each successive three-month period until fully vested.

***Stock-Based Compensation***

The Company recorded \$18.9 million, \$14.3 million and \$11.9 million of stock-based compensation expense for the years ended December 31, 2009, 2008 and 2007, respectively, related to employee stock options and the employee stock purchase plan.

The Company accounts for non-employee grants as an expense over the vesting period of the underlying stock options. At the end of each financial reporting period prior to vesting, the value of these options (as calculated using the Black-Scholes option-pricing model) is re-measured using the then-current fair value of the Company's common stock. The Company recognized \$0.8 million, \$2.1 million and \$2.6 million of non-employee stock-based compensation expense for the years ended December 31, 2009, 2008 and 2007, respectively.

The Company granted the members of Regulus scientific advisory board and board of directors options to purchase 30,000 and 68,500 shares of common stock during 2008 and 2007, respectively. In addition, the Company granted options to purchase 60,000 shares of common stock to two officers of Regulus during 2008 and 60,000 shares of common stock to the chief executive officer of Regulus in 2007. In addition to the total stock-based compensation expense stated above, the Company recorded (\$0.2) million, \$1.6 million and \$0.2 million of stock-based compensation expense related to these option grants in equity in loss of joint venture (Regulus Therapeutics Inc.) in its consolidated statements of operations for the years ended December 31, 2009, 2008 and 2007, respectively.

**Table of Contents****ALNYLAM PHARMACEUTICALS, INC.****NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

Regulus became a C corporation on January 2, 2009. Upon conversion to a C corporation, certain options granted to the members of Regulus' scientific advisory board and board of directors in 2008 and 2007 were forfeited. In addition, upon conversion to a C corporation, certain options granted to two officers and the chief executive officer of Regulus were also forfeited. Prior expense recognized for forfeited shares was reversed in 2009.

In connection with the closing of the sale of Roche Kulmbach to Roche, the Company granted 95,109 shares of restricted stock of the Company to certain employees of Roche Kulmbach. In connection with the closing, the Company also accelerated 177,233 of unvested outstanding stock options of certain Alnylam Europe employees. The Company recorded \$3.8 million of stock-based compensation expense during 2007 related to the restricted stock grants and the stock option modifications.

Total compensation cost for all stock-based payment arrangements for the years ended December 31, 2009, 2008 and 2007 was \$19.5 million, \$18.0 million and \$14.7 million, respectively. No amounts relating to the stock-based compensation have been capitalized.

***Valuation Assumptions for Stock Plans and Employee Stock Purchase Plan***

The fair value of stock options at date of grant, based on the following assumptions, was estimated using the Black-Scholes option-pricing model. The Company's expected stock-price volatility assumption for 2009, 2008 and the three months ended December 31, 2007 is based on a combination of implied volatilities of its publicly traded stock option prices as well as the historical volatility of the Company's publicly traded stock. During the nine months ended September 30, 2007, the Company's expected stock-price volatility assumption was based on a combination of implied volatilities of similar entities whose share or option prices are publicly available as well as the historical volatility of the Company's publicly traded stock. The expected life assumption for 2009, 2008 and for the three months ended December 31, 2007 is based on the equal weighting of the Company's historical data and the historical data of the Company's pharmaceutical and biotechnology peers. During the nine months ended September 30, 2007, the expected life assumption was based on the simplified method, which averages the contractual term of the Company's options (ten years) with the ordinary vesting term (2.2 years). The dividend yield assumption is based on the fact that the Company has never paid cash dividends and has no present intention to pay cash dividends. The risk-free interest rate used for each grant is equal to the zero coupon rate for instruments with a similar expected life. The Company currently expects, based on an analysis of its historical forfeitures, that approximately 83% of its options will actually vest, and therefore have applied an annual forfeiture rate of 4.5% to all unvested options as of December 31, 2009. The Company will record additional expense if the actual forfeitures are lower than estimated and will record a recovery of prior expense if the actual forfeitures are higher than estimated.

	<b>2009</b>	<b>2008</b>	<b>2007</b>
Risk-free interest rate	2.0-3.0%	1.5-3.5%	4.4-4.7%
Expected dividend yield			
Expected option life	6.1-6.3 years	5.7-6.3 years	6.0-6.1 years
Expected volatility	53-66%	66-67%	64-67%

At December 31, 2009, there remained \$44.7 million of unearned compensation expense related to unvested employee stock options to be recognized as expense over a weighted-average period of approximately 1.5 years.



**Table of Contents****ALNYLAM PHARMACEUTICALS, INC.****NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)*****Stock Option Activity***

The following table summarizes the activity of the Company's stock option plans:

	<b>Number of Options</b>	<b>Weighted Average Exercise Price</b>
Outstanding, December 31, 2008	7,037,214	\$ 19.87
Granted	1,650,088	\$ 17.63
Exercised	(275,908)	\$ 5.30
Cancelled	(484,741)	\$ 27.52
Outstanding, December 31, 2009	7,926,653	\$ 19.44
Exercisable at December 31, 2007	1,913,468	\$ 7.49
Exercisable at December 31, 2008	2,903,479	\$ 12.87
Exercisable at December 31, 2009	4,113,776	\$ 17.14

The weighted average remaining contractual life for options outstanding and exercisable at December 31, 2009 was 7.7 years and 6.6 years, respectively.

The aggregate intrinsic value of options outstanding at December 31, 2009 was \$20.9 million, of which \$19.2 million related to exercisable options. The intrinsic value of options exercised was \$4.3 million, \$8.2 million and \$24.6 million for the years ended December 31, 2009, 2008 and 2007, respectively. The weighted average fair value of stock options granted was \$9.84, \$15.02 and \$16.58 per share for the years ended December 31, 2009, 2008 and 2007, respectively.

The aggregate intrinsic value of options expected to vest at December 31, 2009 and 2008 was \$1.6 million and \$10.6 million, respectively. The weighted average fair value of stock options expected to vest was \$12.56 and \$12.10 per share as of December 31, 2009 and 2008, respectively. The weighted average remaining contractual life for options expected to vest at December 31, 2009 and 2008 was 8.3 years and 9.0 years, respectively, and the weighted average exercise price for these options was \$21.92 and \$24.76 per share on December 31, 2009 and 2008, respectively.

***Restricted Stock Awards***

The following table summarizes the activity of the Company's restricted stock awards:

**Weighted  
Average**

	<b>Number of Awards</b>	<b>Grant Date Fair Value</b>
Unvested at December 31, 2008	28,518	\$ 25.98
Granted		\$
Vested	(28,518)	\$ 25.98
Forfeited		\$
Unvested at December 31, 2009		\$

The total fair value of restricted stock awards that vested during the years ended December 31, 2009, 2008 and 2007 was \$0.7 million, \$0.7 million and \$1.0 million, respectively. The Company did not have any unvested or unissued restricted stock awards at December 31, 2009.

**Table of Contents****ALNYLAM PHARMACEUTICALS, INC.****NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)*****Employee Stock Purchase Plan***

In 2004, the Company adopted the 2004 Employee Stock Purchase Plan (the 2004 Purchase Plan ) with 315,789 shares authorized for issuance. Under the 2004 Purchase Plan as adopted, the Company made one offering each year, at the end of which employees could purchase shares of common stock through payroll deductions made over the term of the offering. Initially, the annual offering period began on the 1st day of November each year and ended on the 31st day of October the following year. In June 2007, the compensation committee of the Board of Directors amended the offering period of the 2004 Purchase Plan to provide that each offering period will be for a period of six months, beginning with the offering period commencing on November 1, 2007. The per-share purchase price at the end of the offering is equal to the lesser of 85% of the closing price of the common stock at the beginning or end of the offering period. The Company issued 59,267, 35,065 and 29,723 shares during the years ended December 31, 2009, 2008 and 2007, respectively, and as of December 31, 2009, 99,412 shares were available for issuance under the 2004 Purchase Plan.

The weighted average fair value of stock purchase rights granted as part of the 2004 Purchase Plan was \$7.20, \$9.51 and \$10.61 per share for the years ended December 31, 2009, 2008 and 2007, respectively. The fair value was estimated using the Black-Scholes option-pricing model. The Company used a weighted-average stock-price volatility of 66%, expected option life assumption of six months and a risk-free interest rate of 0.7%. The Company recorded \$0.4 million, \$0.3 million and \$0.2 million of stock-based compensation expense for the years ended December 31, 2009, 2008 and 2007, respectively, related to the 2004 Purchase Plan.

**10. INCOME TAXES**

Deferred income taxes reflect the tax effects of temporary differences between the carrying amounts of assets and liabilities for financial reporting and income tax purposes. A valuation allowance is established when uncertainty exists as to whether all or a portion of the net deferred tax assets will be realized. Components of the net deferred tax asset (liability) as of December 31, 2009, 2008 and 2007 are as follows, in thousands:

	<b>2009</b>	<b>2008</b>	<b>2007</b>
Deferred tax assets:			
Net operating loss carryforwards	\$ 496	\$ 496	\$ 49,910
Research and development credits		298	3,582
Foreign tax credits			3,072
Capitalized research and development and start-up costs	7,729	9,558	12,750
Deferred revenue	92,811	74,423	2,745
Deferred compensation	12,433	7,532	3,237
Intangible assets	9,551	5,422	1,540
Partnership interest	2,666	756	
Other	1,037	1,930	3,674
Total deferred tax assets	126,723	100,415	80,510
Deferred tax liabilities:			

Edgar Filing: ALNYLAM PHARMACEUTICALS, INC. - Form 10-K

Intangible assets	(194)	(246)	(365)
Deferred tax asset valuation allowance	(116,230)	(95,033)	(80,510)
Net deferred tax asset (liability)	\$ 10,299	\$ 5,136	\$ (365)

**Table of Contents****ALNYLAM PHARMACEUTICALS, INC.****NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

The provision for income taxes for the years ended December 31, 2009 and 2008 was as follows, in thousands:

	<b>2009</b>	<b>2008</b>
U.S.:		
Current	\$ 5,987	\$ 5,978
Deferred	(5,111)	(5,382)
Total U.S.	876	596
Foreign:		
Current	(242)	242
Deferred	(52)	(119)
Total Foreign	(294)	123
Provision for income taxes	\$ 582	\$ 719

The Company's effective income tax rate differs from the statutory federal income tax rate as follows for the years ended December 31, 2009, 2008 and 2007:

	<b>2009</b>	<b>2008</b>	<b>2007</b>
At U.S. federal statutory rate	35.0%	35.0%	34.0%
State taxes, net of federal effect	(0.6)	(0.5)	5.8
Foreign tax credit			3.8
Foreign dividends			(6.6)
Stock compensation	(4.2)	(6.0)	(2.4)
Other	(0.3)	(0.3)	
Other permanent items	0.1	(0.3)	1.6
Deemed gain on Roche Germany transaction			(6.3)
Research credits			0.4
Valuation allowance	(31.3)	(30.7)	(36.7)
Effective income tax rate	(1.3)%	(2.8)%	(6.4)%

The Company has evaluated the positive and negative evidence bearing upon the realizability of its deferred tax assets. The Company has concluded, in accordance with the applicable accounting standards, that it is more likely than not that the Company may not realize the benefit of all its deferred tax assets. Accordingly, a valuation allowance has been recorded against the deferred tax assets that management believes will not be realized. The Company

reevaluates the positive and negative evidence on a quarterly basis. The valuation allowance increased by \$21.2 million, \$14.5 million and \$29.6 million for the years ended December 31, 2009, 2008 and 2007, respectively, due primarily to recognition of deferred revenue for tax purposes.

During 2009 and 2008, the Company utilized certain tax attributes, including net operating loss and tax credit carryforwards as a result of the recognition of revenue for certain proceeds received from strategic alliances. However, the Company also generated a deferred tax asset related to the recognition of this revenue for tax purposes. As a result, the Company has recorded a net deferred tax asset to the extent it is more likely than not that the asset will be realized. The remaining deferred tax assets are subject to a valuation allowance as it is more likely than not that those assets will not be realized.

The deferred tax assets above exclude \$9.5 million of deductions related to the exercise of stock options subsequent to the adoption of the 2006 accounting standard on stock based compensation. This amount represents an excess tax benefit and has not been included in the gross deferred tax assets. At December 31, 2009, the Company

**Table of Contents**

**ALNYLAM PHARMACEUTICALS, INC.**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

had \$2.2 million of state research and development tax credit carryforwards derived from stock option exercises that are available to reduce future Massachusetts tax liabilities.

At December 31, 2009, the state net operating loss carryforward was \$8.6 million. This attribute is available to reduce the Company's future California state tax liability and expires at various dates through 2018. 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 that can be utilized to offset future taxable income or tax liability. The Company has determined that there is no limitation on the utilization of net operating loss carryforwards in accordance with Section 382 of the Internal Revenue Code in 2009.

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 December 31, 2009, the Company had no unrecognized tax benefits.

The tax years 2002 through 2008 remain open to examination by major taxing jurisdictions to which the Company is subject, which are primarily in the United States, as carryforward attributes generated in years past may still be adjusted upon examination by the Internal Revenue Service or state tax authorities if they have or will be used in a future period. The Company is currently not under examination by the Internal Revenue Service or any other jurisdictions for any tax years. The Company recognizes both accrued interest and penalties related to unrecognized benefits in income tax expense. The Company has not recorded any interest and penalties on any unrecognized tax benefits since its inception.

**11. 401(K) SAVINGS PLAN**

The Company sponsors a savings plan for its employees in the United States, who meet certain eligibility requirements, which is designed to be a qualified plan under section 401(k) of the Internal Revenue Code (the 401(k) Plan). Participants may contribute up to 60% of their annual base salary to the 401(k) Plan, subject to certain limitations. Beginning in April 2006, the Company began matching in its common stock up to 3% of a participant's base salary. Employer common stock matches vest anywhere from immediately to two years, depending on years of service with the Company. Employees have the ability to transfer funds from the Company stock fund to other plan funds as they choose, subject to blackout periods. The Company issued 22,502, 14,679 and 12,706 shares of common stock during the years ended December 31, 2009, 2008 and 2007, respectively, in connection with matching contributions under the 401(k) Plan.

**12. REGULUS**

In September 2007, the Company and Isis established Regulus, a company focused on the discovery, development and commercialization of microRNA-based therapeutics, a potential new class of drugs to treat the pathways of human disease. Regulus, which initially was established as a limited liability company, converted to a C corporation in January 2009 and changed its name to Regulus Therapeutics Inc.

In consideration for the Company's and Isis' initial interests in Regulus, each party granted Regulus exclusive licenses to its intellectual property for certain microRNA-based therapeutic applications as well as certain patents in the microRNA field. In addition, the Company made an initial cash contribution to Regulus of \$10.0 million, resulting in

the Company and Isis making approximately equal aggregate initial capital contributions to Regulus. Additionally, in March 2009, the Company and Isis each purchased \$10.0 million of Series A preferred stock of Regulus under the Investor Rights Agreement. The Company and Isis currently own approximately 49% and 51%, respectively, of Regulus and there are currently no other third party investors in Regulus. Regulus continues to operate as an independent company with a separate board of directors, scientific advisory board and management team, some of whom have options to purchase common stock of Regulus. Members of the board of directors of Regulus who are employees of the Company or Isis are not eligible to receive options to purchase Regulus common stock.



**Table of Contents**

**ALNYLAM PHARMACEUTICALS, INC.**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

The Company, Isis and Regulus also entered into a license and collaboration agreement (the Regulus Collaboration Agreement ) to pursue the discovery, development and commercialization of therapeutic products directed to microRNAs. Under the terms of the Regulus Collaboration Agreement, the Company and Isis each assigned to Regulus specified patents and contracts covering microRNA-specific technology. In addition, each of the Company and Isis granted to Regulus an exclusive, worldwide license under its rights to other microRNA-related patents and know-how to develop and commercialize therapeutic products containing compounds that are designed to interfere with or inhibit a particular microRNA, subject to the Company's and Isis' existing contractual obligations to third parties. Regulus was also granted the right to request a license from the Company and Isis to develop and commercialize therapeutic products directed to other microRNA compounds, which license is subject to the Company's and Isis' approval and to each such party's existing contractual obligations to third parties. Regulus also granted to the Company and Isis an exclusive license to technology developed or acquired by Regulus for use solely within the Company's and Isis' respective fields (as defined in the Regulus Collaboration Agreement), but specifically excluding the right to develop, manufacture or commercialize the therapeutic products for which the Company and Isis granted rights to Regulus.

The Regulus Collaboration Agreement ends if, prior to first commercial sale of any product, all development activities cease under the collaboration. The Regulus Collaboration Agreement otherwise expires, on a product-by-product and country-by-country basis, upon the later of expiration of marketing exclusivity for such product or a specified number of years from first commercial sale. If Regulus, the Company or Isis commits an uncured material breach of the Regulus Collaboration Agreement, the Regulus Collaboration Agreement may be terminated with respect to the breaching party or a buy-out may be initiated, depending on the nature of the breach.

In September 2007, the Company and Isis also executed a Services Agreement (the Services Agreement ) with Regulus. Under the terms of the Services Agreement, the Company and Isis provide to Regulus, for the benefit of Regulus, certain research and development and general and administrative services for which they are paid by Regulus.

In April 2008, Regulus 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 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 common stock under certain specified circumstances. Regulus 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 would also receive royalty payments on worldwide sales of products resulting from the alliance, if any.

In February 2010, Regulus and GSK established a new collaboration to develop and commercialize microRNA-based therapeutics targeting miR-122 in all fields, with hepatitis C virus infection as the lead indication. This new collaboration includes the potential for Regulus to earn more than \$150.0 million in upfront and milestone payments, in addition to royalties, on worldwide sales of products, if any, as Regulus and GSK advance microRNA-based therapeutics targeting miR-122.

The Company has reviewed the consolidation guidance that defines a VIE and concluded that Regulus currently qualifies as a VIE. The Investor Rights Agreement contains transfer restrictions on each of Isis' and the Company's

interests and, as a result, Isis and the Company are considered related parties under the consolidation guidance. The Company has assessed which entity would be considered the primary beneficiary under the consolidation guidance and has concluded that Isis is the primary beneficiary and, accordingly, the Company has not consolidated Regulus.

The Company accounts for its investment in Regulus using the equity method of accounting. Through December 31, 2008, the Company was recognizing the first \$10.0 million of losses of Regulus as equity in loss of joint venture (Regulus Therapeutics Inc.) in its consolidated statements of operations because the Company was responsible for funding those losses through its initial \$10.0 million cash contribution. Beginning in January 2009,

**Table of Contents****ALNYLAM PHARMACEUTICALS, INC.****NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

in connection with the conversion of Regulus to a C corporation, the Company is recognizing approximately 49% of the income and losses of Regulus. The carrying value of the Company's investment in joint venture (Regulus Therapeutics Inc.) immediately prior to the conversion to a C corporation exceeded 49% of the net assets of Regulus by approximately \$0.8 million. Upon conversion, this amount was allocated to the intellectual property of Regulus and, because the intellectual property was determined to be in-process research and development, the \$0.8 million was recorded as a charge to expense. This charge is included in equity in loss of joint venture (Regulus Therapeutics Inc.) in the consolidated statements of operations for the year ended December 31, 2009. Under the equity method, the reimbursement of expenses to the Company is recorded as a reduction to research and development expenses. At December 31, 2009, the Company's investment in the joint venture was \$6.4 million, which is recorded as an investment in joint venture (Regulus Therapeutics Inc.) in the consolidated balance sheets under the equity method. Summary results of Regulus' operations for the years ended December 31, 2009, 2008 and 2007 and balance sheets as of December 31, 2009 and 2008 are presented in the table below, in thousands:

	<b>2009</b>	<b>2008</b>	<b>2007</b>
<b>Statement of Operations Data:</b>			
Net revenues	\$ 3,013	\$ 2,111	\$ 120
Operating expenses(1)	11,789	12,029	1,541
Loss from operations	(8,776)	(9,918)	(1,421)
Other income	13	256	138
Income tax expense	(141)		
Net loss	\$ (8,904)	\$ (9,662)	\$ (1,283)
(1) Non-cash stock-based compensation expenses included in operating expenses	\$ 99	\$ 2,017	\$ 412

	<b>2009</b>	<b>2008</b>
<b>Balance Sheet Data:</b>		
Cash and cash equivalents	\$ 16,228	\$ 22,411
Working capital	25,115	16,467
Total assets	32,930	23,678
Notes payable	6,291	5,179
Total stockholders' equity	12,939	1,745

Separate financial information for Regulus is included in Exhibit 99.1 to this annual report on Form 10-K.



Table of Contents

## ALNYLAM PHARMACEUTICALS, INC.

## NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

## 13. QUARTERLY FINANCIAL DATA (UNAUDITED)

The following information has been derived from unaudited consolidated financial statements that, in the opinion of management, include all recurring adjustments necessary for a fair presentation of such information.

	Three Months Ended			
	March 31, 2009	June 30, 2009	September 30, 2009	December 31, 2009
	(In thousands, except per share data)			
Revenues	\$ 25,057	\$ 24,601	\$ 24,249	\$ 26,626
Operating expenses	33,037	47,013	33,899	34,695
Net loss	(7,889)	(22,702)	(9,208)	(7,791)
Net loss per common share basic and diluted	\$ (0.19)	\$ (0.55)	\$ (0.22)	\$ (0.19)
Weighted average common shares basic and diluted	41,399	41,520	41,708	41,812

	Three Months Ended			
	March 31, 2008	June 30, 2008	September 30, 2008	December 31, 2008
	(In thousands, except per share data)			
Revenues	\$ 22,192	\$ 23,833	\$ 25,734	\$ 24,404
Operating expenses	26,149	36,664	28,968	32,217
Net loss	(1,239)	(12,760)	(2,858)	(9,392)
Net loss per common share basic and diluted	\$ (0.03)	\$ (0.31)	\$ (0.07)	\$ (0.23)
Weighted average common shares basic and diluted	40,736	40,908	41,197	41,375

**Table of Contents**

**ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE**

None.

**ITEM 9A. 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 December 31, 2009. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company's management, including its principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of December 31, 2009, the Company's 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.

Management's report on our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) and the independent registered public accounting firm's report on the effectiveness of our internal control over financial reporting are included in Item 8 of this annual report on Form 10-K and are incorporated herein by reference.

No change in our internal control over financial reporting occurred during the fiscal quarter ended December 31, 2009 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

**ITEM 9B. OTHER INFORMATION**

None.

**PART III**

**ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE**

The information required by this item is incorporated herein by reference to the information contained under the sections captioned "Proposal One Election of Class I Directors," "Section 16(a) Beneficial Ownership Reporting Compliance" and "Corporate Governance" of the Proxy Statement. The information required by this item relating to executive officers is included in "Part I, Item 1 Business- Executive Officers of the Registrant" of this annual report on Form 10-K.

**ITEM 11. EXECUTIVE COMPENSATION**

The information required by this item is incorporated herein by reference to the information contained under the sections captioned "Information about Executive Officer and Director Compensation," "Compensation Committee

Interlocks and Insider Participation , Employment Arrangements and Compensation Committee Report of the Proxy Statement.

**Table of Contents**

**ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS**

The information required by this item is incorporated herein by reference to the information contained under the sections captioned Security Ownership of Certain Beneficial Owners and Management Information about Executive Officer and Director Compensation and Securities Authorized for Issuance Under Equity Compensation Plans of the Proxy Statement.

**ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE**

The information required by this item is incorporated herein by reference to the information contained under the sections captioned Corporate Governance, Employment Arrangements and Certain Relationships and Related Transactions of the Proxy Statement.

**ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES**

The information required by this item is incorporated herein by reference to the information contained under the sections captioned Corporate Governance, Principal Accountant Fees and Services and Pre-Approval Policies and Procedures of the Proxy Statement.

**PART IV**

**ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES**

(a) (1) Financial Statements

The following consolidated financial statements are filed as part of this report under Item 8 Financial Statements and Supplementary Data :

	<b>Page</b>
<u>Management's Annual Report on Internal Control Over Financial Reporting</u>	103
<u>Report of Independent Registered Public Accounting Firm</u>	104
<u>Consolidated Balance Sheets as of December 31, 2009 and 2008</u>	105
<u>Consolidated Statements of Operations and Comprehensive Loss for the Years Ended December 31, 2009, 2008 and 2007</u>	106
<u>Consolidated Statements of Stockholders' Equity for the Years Ended December 31, 2007, 2008 and 2009</u>	107
<u>Consolidated Statements of Cash Flows for the Years Ended December 31, 2009, 2008 and 2007</u>	108
<u>Notes to Consolidated Financial Statements</u>	109

(a) (2) List of Schedules

All schedules to the consolidated financial statements are omitted as the required information is either inapplicable or presented in the consolidated financial statements.

(a) (3) List of Exhibits



The exhibits which are filed with this report or which are incorporated herein by reference are set forth in the Exhibit Index hereto.

**Table of Contents**

**SIGNATURES**

Pursuant to the requirements of Section 13 or 15(d) 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, on February 26, 2010.

ALNYLAM PHARMACEUTICALS, INC.

By: /s/ John M. Maraganore, Ph.D.

John M. Maraganore, Ph.D.  
Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, the Report has been signed below by the following persons on behalf of the Registrant and in the capacities indicated as of February 26, 2010.

<b>Name</b>	<b>Title</b>
/s/ John M. Maraganore, Ph.D. John M. Maraganore, Ph.D.	Director and Chief Executive Officer (Principal Executive Officer)
/s/ Patricia L. Allen Patricia L. Allen	Vice President of Finance and Treasurer (Principal Financial and Accounting Officer)
/s/ John K. Clarke John K. Clarke	Director
/s/ Victor J. Dzau, M.D. Victor J. Dzau, M.D.	Director
/s/ Vicki L. Sato, Ph.D. Vicki L. Sato, Ph.D.	Director
/s/ Paul R. Schimmel, Ph.D. Paul R. Schimmel, Ph.D.	Director
/s/ Edward M. Scolnick, M.D. Edward M. Scolnick, M.D.	Director
/s/ Phillip A. Sharp, Ph.D.	Director

Phillip A. Sharp, Ph.D.

/s/ Kevin P. Starr

Director

Kevin P. Starr

/s/ James L. Vincent

Director

James L. Vincent

**Table of Contents****EXHIBIT INDEX**

<b>Exhibit No.</b>	<b>Exhibit</b>
3.1	Restated Certificate of Incorporation of the Registrant (filed as Exhibit 3.1 to the Registrant's Quarterly Report on Form 10-Q filed on August 11, 2005 (File No. 000-50743) for the quarterly period ended June 30, 2005 and incorporated herein by reference)
3.2	Amended and Restated Bylaws of the Registrant (filed as Exhibit 3.4 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
4.1	Specimen certificate evidencing shares of common stock (filed as Exhibit 4.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
4.2	Rights Agreement dated as of July 13, 2005 between the Registrant and EquiServe Trust Company, N.A., as Rights Agent, which includes as Exhibit A the Form of Certificate of Designations of Series A Junior Participating Preferred Stock, as Exhibit B the Form of Rights Certificate and as Exhibit C the Summary of Rights to Purchase Preferred Stock (filed as Exhibit 4.1 to the Registrant's Current Report on Form 8-K filed on July 14, 2005 (File No. 000-50743) and incorporated herein by reference)
10.1*	2002 Employee, Director and Consultant Stock Plan, as amended, together with forms of Incentive Stock Option Agreement, Non-qualified Stock Option Agreement and Restricted Stock Agreement (filed as Exhibit 10.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.2*	2003 Employee, Director and Consultant Stock Plan, as amended, together with forms of Incentive Stock Option Agreement, Non-qualified Stock Option Agreement and Restricted Stock Agreement (filed as Exhibit 10.2 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.3*	Amended and Restated 2004 Stock Incentive Plan (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on August 7, 2009 (File No. 000-50743) for the quarterly period ended June 30, 2009 and incorporated herein by reference)
10.4*	Forms of Incentive Stock Option Agreement and Nonstatutory Stock Option Agreement under 2004 Stock Incentive Plan, as amended (filed as Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q filed on August 11, 2005 (File No. 000-50743) for the quarterly period ended June 30, 2005 and incorporated herein by reference)
10.5*	Form of Nonstatutory Stock Option Agreement under 2004 Stock Incentive Plan granted to John M. Maraganore, Ph.D., on December 21, 2004 (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on December 28, 2004 (File No. 000-50743) and incorporated herein by reference)
10.6*	Form of Nonstatutory Stock Option Agreement under 2004 Stock Incentive Plan granted to James L. Vincent on July 12, 2005 (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on July 13, 2005 (File No. 000-50743) and incorporated herein by reference)
10.7*	Form of Restricted Stock Agreement under 2004 Stock Incentive Plan issued to James L. Vincent on July 12, 2005 (filed as Exhibit 10.2 to the Registrant's Current Report on Form 8-K filed on July 13, 2005 (File No. 000-50743) and incorporated herein by reference)
10.8*	2009 Stock Incentive Plan (filed as Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed on August 7, 2009 (File No. 000-50743) for the quarterly period ended June 30, 2009 and incorporated herein by reference)
10.9*#	Forms of Incentive Stock Option Agreement and Nonstatutory Stock Option Agreement under 2009 Stock Incentive Plan
10.10	Investor Rights Agreement entered into as of March 11, 2004 by and between the Registrant and Isis Pharmaceuticals, Inc. (filed as Exhibit 10.25 to the Registrant's Registration Statement on Form S-1

(File No. 333-113162) and incorporated herein by reference)

- 10.11 Stock Purchase Agreement, dated as of September 6, 2005, by and between the Registrant and Novartis Pharma AG (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on September 12, 2005 (File No. 000-50743) and incorporated herein by reference)
- 10.12 Investor Rights Agreement, dated as of September 6, 2005, by and between the Registrant. and Novartis Pharma AG (filed as Exhibit 10.2 to the Registrant's Current Report on Form 8-K filed on September 12, 2005 (File No. 000-50743) and incorporated herein by reference)

**Table of Contents**

<b>Exhibit No.</b>	<b>Exhibit</b>
10.13*	Letter Agreement between the Registrant and John M. Maraganore, Ph.D. dated October 30, 2002 (filed as Exhibit 10.7 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.14*	Letter Agreement between the Registrant and Barry E. Greene dated September 29, 2003 (filed as Exhibit 10.10 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.15*	Letter Agreement between the Registrant and John A. Schmidt, M.D. (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on November 4, 2009 (File No. 000-50743) for the quarterly period ended September 30, 2009 and incorporated herein by reference)
10.16*#	2010 Annual Incentive Program
10.17	Lease, dated as of September 26, 2003 by and between the Registrant and Three Hundred Third Street LLC (filed as Exhibit 10.15 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.18	First Amendment to Lease, dated March 16, 2006, by and between the Registrant and ARE-MA Region No. 28, LLC (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on March 17, 2006 (File No. 000-50743) and incorporated herein by reference)
10.19	Second Amendment to Lease, dated June 26, 2009, by and between the Registrant and ARE-MA Region No. 28, LLC (filed as Exhibit 10.4 to the Registrant's Quarterly Report on Form 10-Q filed on August 7, 2009 (File No. 000-50743) for the quarterly period ended June 30, 2009 and incorporated herein by reference)
10.20	License Agreement between Cancer Research Technology Limited and Alnylam U.S., Inc. dated July 18, 2003 (filed as Exhibit 10.16 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.21	License Agreement between the Carnegie Institution of Washington and Alnylam Europe, AG, effective March 1, 2002, as amended by letter agreements dated September 2, 2002 and October 28, 2003 (filed as Exhibit 10.17 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.22	License Agreement by and between the Cold Spring Harbor Laboratory and Alnylam U.S., Inc. dated December 30, 2003 (filed as Exhibit 10.18 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.23	Co-exclusive License Agreement between Garching Innovation GmbH (now known as Max Planck Innovation GmbH) and Alnylam U.S., Inc. dated December 20, 2002, as amended by Amendment dated July 8, 2003 together with Indemnification Agreement by and between Garching Innovation GmbH (now known as Max Planck Innovation GmbH) and Alnylam Pharmaceuticals, Inc. effective April 1, 2004 (filed as Exhibit 10.19 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.24	Co-exclusive License Agreement between Garching Innovation GmbH (now known as Max Planck Innovation GmbH) and Alnylam Europe, AG dated July 30, 2003 (filed as Exhibit 10.20 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.25	Agreement between the Registrant, Garching Innovation GmbH (now known as Max Planck Innovation GmbH), Alnylam U.S., Inc. and Alnylam Europe AG dated June 14, 2005 (filed as Exhibit 10.8 to the Registrant's Quarterly Report on Form 10-Q filed on August 11, 2005 (File No. 000-50743) for the quarterly period ended June 30, 2005 and incorporated herein by reference)
10.26	Agreement between The Board of Trustees of the Leland Stanford Junior University and Alnylam U.S., Inc. effective as of September 17, 2003 (filed as Exhibit 10.21 to the Registrant's Registration

- 10.27 Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)  
Research Collaboration and License Agreement effective as of October 12, 2005 by and between the Registrant and Novartis Institutes for BioMedical Research, Inc. (filed as Exhibit 10.23 to the Registrant's Annual Report on Form 10-K filed on March 2, 2009 (File No. 000-50743) for the quarterly and annual period ended December 31, 2008)

**Table of Contents**

<b>Exhibit No.</b>	<b>Exhibit</b>
10.28	Collaboration and License Agreement dated September 20, 2006, by and between the Registrant and Biogen Idec Inc. (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on November 9, 2006 (File No. 000-50743) for the quarterly period ended September 30, 2006 and incorporated herein by reference)
10.29	License and Collaboration Agreement, entered into as of July 8, 2007, by and among F. Hoffmann-La Roche, Ltd, Hoffmann-La Roche Inc., the Registrant and, for limited purposes, Alnylam Europe AG (filed as Exhibit 10.26 to the Registrant's Annual Report on Form 10-K filed on March 2, 2009 (File No. 000-50743) for the quarterly and annual period ended December 31, 2008)
10.30	Common Stock Purchase Agreement dated as of July 8, 2007 between the Registrant and Roche Finance Ltd (filed as Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed on November 8, 2007 (File No. 000-50743) for the quarterly period ended September 30, 2007 and incorporated herein by reference)
10.31	Share Purchase Agreement, dated as of July 8, 2007, among Alnylam Europe AG, the Registrant and Roche Pharmaceuticals GmbH (filed as Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q filed on November 8, 2007 (File No. 000-50743) for the quarterly period ended September 30, 2007 and incorporated herein by reference)
10.32	Amended and Restated Collaboration Agreement, entered into as of July 27, 2007, by and between the Registrant and Medtronic, Inc. (filed as Exhibit 10.4 to the Registrant's Quarterly Report on Form 10-Q filed on November 8, 2007 (File No. 000-50743) for the quarterly period ended September 30, 2007 and incorporated herein by reference)
10.33	Termination Agreement, dated as of September 18, 2007, by and between Merck & Co., Inc. and the Registrant (filed as Exhibit 10.7 to the Registrant's Quarterly Report on Form 10-Q filed on November 8, 2007 (File No. 000-50743) for the quarterly period ended September 30, 2007 and incorporated herein by reference)
10.34	License and Collaboration Agreement entered into as of May 27, 2008 by and among Takeda Pharmaceutical Company Limited and the Registrant (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on August 8, 2008 (File No. 000-50743) for the quarterly period ended June 30, 2008 and incorporated herein by reference)
10.35	License and Collaboration Agreement entered into as of January 9, 2009 by and between the Registrant and Cubist Pharmaceuticals, Inc. (filed as Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed on May 8, 2009 (File No. 000-50743) for the quarterly period ended March 31, 2009 and incorporated herein by reference)
10.36	Amended and Restated License and Collaboration Agreement, entered into as of January 1, 2009, by and among the Registrant, Isis Pharmaceuticals, Inc. and Regulus Therapeutics Inc. (filed as Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q filed on May 8, 2009 (File No. 000-50743) for the quarterly period ended March 31, 2009 and incorporated herein by reference)
10.37	Founding Investor Rights Agreement entered into as of January 1, 2009, by and among Regulus Therapeutics Inc., Isis Pharmaceuticals, Inc. and the Registrant (filed as Exhibit 10.4 to the Registrant's Quarterly Report on Form 10-Q filed on May 8, 2009 (File No. 000-50743) for the quarterly period ended March 31, 2009 and incorporated herein by reference)
10.38	Amended and Restated Strategic Collaboration and License Agreement effective as of April 28, 2009 between Isis Pharmaceuticals, Inc. and the Registrant (filed as Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q filed on August 7, 2009 (File No. 000-50743) for the quarterly period ended June 30, 2009 and incorporated herein by reference)
10.39 #	Collaboration Agreement entered into as of October 29, 2009 by and among F. Hoffmann-La Roche Ltd, Hoffmann-La Roche Inc. and the Registrant



Edgar Filing: ALNYLAM PHARMACEUTICALS, INC. - Form 10-K

- 10.40 # First Amendment to License and Collaboration Agreement entered into as of November 2, 2009 by and between the Registrant and Cubist Pharmaceuticals, Inc.
- 21.1# Subsidiaries of the Registrant
- 23.1# Consent of PricewaterhouseCoopers LLP, Independent Registered Public Accounting Firm

**Table of Contents**

<b>Exhibit No.</b>	<b>Exhibit</b>
23.2#	Consent of Ernst & Young LLP, Independent Auditors of Regulus Therapeutics Inc.
31.1#	Certification pursuant to Section 302 of the Sarbanes-Oxley Act of 2002, Rule 13(a)- 14(a)/15d-14(a), by Chief Executive Officer
31.2#	Certification pursuant to Section 302 of the Sarbanes-Oxley Act of 2002, Rule 13(a)- 14(a)/15d-14(a), by Vice President of Finance and Treasurer
32.1#	Certification pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, by Chief Executive Officer
32.2#	Certification pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, by Vice President of Finance and Treasurer
99.1#	Regulus Therapeutics Inc. s Financial Statements

\* Management contracts or compensatory plans or arrangements required to be filed as an exhibit hereto pursuant to Item 15(a) of Form 10-K.

Indicates confidential treatment requested as to certain portions, which portions were omitted and filed separately with the Securities and Exchange Commission pursuant to a Confidential Treatment Request.

# Filed herewith.