ALNYLAM PHARMACEUTICALS, INC.
Form 424B5
February 13, 2012
**Table of Contents**

**Filed Pursuant to Rule 424(b)(5)**
**Registration No. 333-175694**

**The information in this preliminary prospectus supplement is not complete and may be changed. A registration statement relating to these securities has been declared effective by the Securities and Exchange Commission. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities, and we are not soliciting offers to buy these securities in any jurisdiction where the offer or sale is not permitted.**

**Subject to completion, dated February 13, 2012**

**Preliminary Prospectus Supplement (To Prospectus dated August 19, 2011)**

# *7,000,000 shares*

# *Common Stock*

We are offering 7,000,000 shares of our common stock.

Our common stock trades on the NASDAQ Global Market under the trading symbol ALNY . On February 10, 2012, the last reported sale price of our common stock on the NASDAQ Global Market was $12.15 per share.

| | Per Share | Total |
|---|---|---|
| Public offering price | $ | $ |
| Underwriting discounts and commissions | $ | $ |
| Proceeds, before expenses, to us | $ | $ |

We have granted the underwriter an option for a period of 30 days from the date of this prospectus supplement to purchase up to 1,050,000 additional shares of our common stock at the public offering price less the underwriting discounts and commissions solely to cover over-allotments, if any.

**Investing in our common stock involves risks. See Risk Factors beginning on page S-8 of this prospectus supplement.**

**Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus supplement or the accompanying prospectus. Any representation to the contrary is a criminal offense.**

The underwriter expects to deliver the shares to purchasers on or about February , 2012.

*Sole book-running manager*

# J.P. Morgan

**February , 2012**

Table of Contents

# Table of contents

Table of Contents

# About this prospectus supplement

This document consists of two parts. The first part is this prospectus supplement, which describes the specific terms of this common stock offering and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference herein. The second part, the accompanying prospectus, provides more general information. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. To the extent there is a conflict between the information contained in this prospectus supplement and the information contained in the accompanying prospectus or any document incorporated by reference therein filed prior to the date of this prospectus supplement, you should rely on the information in this prospectus supplement; provided that if any statement in one of these documents is inconsistent with a statement in another document having a later date for example, a document incorporated by reference in the accompanying prospectus the statement in the document having the later date modifies or supersedes the earlier statement.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference herein were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

We have not authorized anyone to provide any information other than that contained or incorporated by reference in this prospectus supplement, the accompanying prospectus or in any free writing prospectus prepared by or on behalf of us or to which we have referred you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. This prospectus supplement and the accompanying prospectus do not constitute an offer to sell, or a solicitation of an offer to purchase, the securities offered by this prospectus supplement and the accompanying prospectus in any jurisdiction to or from any person to whom or from whom it is unlawful to make such offer or solicitation of an offer in such jurisdiction. The information contained in this prospectus supplement or the accompanying prospectus, or incorporated by reference herein is accurate only as of the respective dates thereof, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or of any sale of our common stock. It is important for you to read and consider all information contained in this prospectus supplement and the accompanying prospectus, including the documents incorporated by reference herein and therein, in making your investment decision. You should also read and consider the information in the documents to which we have referred you in the sections entitled Where You Can Find More Information and Incorporation of Certain Information by Reference in this prospectus supplement and in the accompanying prospectus.

We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the accompanying prospectus and the offering of the common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement and the accompanying prospectus must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this prospectus supplement and the accompanying prospectus outside the United States. This prospectus supplement and the accompanying prospectus do not constitute, and may not be

Table of Contents

used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement and the accompanying prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

Unless the context otherwise indicates, references in this prospectus to Alnylam, we, our, us, the Company and similar designations refer, collectively, to Alnylam Pharmaceuticals, Inc., a Delaware corporation, and its consolidated subsidiaries. Alnylam is a trademark of Alnylam Pharmaceuticals, Inc. Our logo, trademarks and service marks are property of Alnylam. All other trademarks or service marks appearing in this prospectus supplement are the property of their respective holders.

Table of Contents

# Prospectus supplement summary

*This summary highlights information contained elsewhere in this prospectus supplement and the accompanying prospectus and in the documents we incorporate by reference. This summary does not contain all of the information that you should consider before deciding to invest in our common stock. You should read this entire prospectus supplement and the accompanying prospectus carefully, including the Risk Factors section contained in this prospectus supplement and our consolidated financial statements and the related notes and the other documents incorporated by reference herein.*

## Alnylam Pharmaceuticals, Inc.

## Our business

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

Our core product strategy, which we refer to as Alnylam 5x15, is focused on the development and commercialization of novel RNAi therapeutics for the treatment of genetically defined diseases with high unmet medical need. Under our core product strategy, we expect to have five RNAi therapeutic programs in clinical development, including programs in advanced stages, on our own or with one or more collaborators, by the end of 2015. As part of this strategy, our goal is to develop product candidates with the following shared characteristics: a genetically defined target and disease; the potential to have a significant impact in high unmet need patient populations; the ability to leverage our existing RNAi delivery platform; the opportunity to monitor an early biomarker in Phase I clinical trials for human proof of concept; and the existence of clinically relevant endpoints for the filing of a new drug application, or NDA, with a focused patient database and possible accelerated paths for commercialization. Our core programs currently in clinical or pre-clinical development are: ALN-TTR for the treatment of transthyretin-mediated amyloidosis, or ATTR; ALN-APC for the treatment of hemophilia; ALN-PCS for the treatment of severe hypercholesterolemia; ALN-HPN for the treatment of refractory anemia; and ALN-TMP for the treatment of hemoglobinopathies, including beta-thalassemia and sickle cell anemia. We intend to focus on developing and commercializing ALN-TTR and ALN-APC on our own in the United States and potentially certain other countries, and we intend to enter into alliances to advance our ALN-PCS, ALN-HPN and ALN-TMP programs.

While focusing our efforts on our core product strategy, we also intend to continue to advance additional development programs through existing or future alliances. We have three partner-based programs in clinical or pre-clinical development, including ALN-RSV01 for the treatment of respiratory syncytial virus, or RSV, infection, ALN-VSP for the treatment of liver cancers and ALN-HTT for the treatment of Huntington s disease, or HD.

We also continue to work internally and with third-party collaborators with the goal of developing new technologies to deliver our RNAi therapeutics both directly to specific sites of disease, and systemically by intravenous or subcutaneous administration. We have numerous

Table of Contents

RNAi therapeutic delivery collaborations and intend to continue to collaborate with academic and corporate third parties, as well as government entities, to evaluate different delivery options.

We believe that the strength of our intellectual property portfolio relating to the development and commercialization of small interfering RNAs, or siRNAs, as therapeutics provides us a leading position with respect to this therapeutic modality. Our intellectual property portfolio includes ownership of, or exclusive rights to, issued patents and pending patent applications claiming fundamental features of siRNAs and RNAi therapeutics as well as those claiming crucial chemical modifications and promising delivery technologies. We believe that no other company possesses a portfolio of such broad and exclusive rights to the patents and patent applications required for the commercialization of RNAi therapeutics. Given the importance of our intellectual property portfolio to our business operations, we intend to vigorously enforce our rights and defend against challenges that have arisen or may arise in this area.

In addition, our expertise in RNAi therapeutics and broad intellectual property estate have allowed us to form alliances with leading pharmaceutical companies, including Isis Pharmaceuticals, Inc., or Isis, Medtronic, Inc., or Medtronic, Novartis Pharma AG, or Novartis, Biogen Idec Inc., F. Hoffmann-La Roche Ltd, or Roche (which assigned its rights and obligations to Arrowhead Research Corporation, or Arrowhead during 2011), Takeda Pharmaceutical Company Limited, or Takeda, Kyowa Hakko Kirin Co., Ltd., or Kyowa Hakko Kirin, and Cubist Pharmaceuticals, Inc., or Cubist. We have previously entered, and in the future, we intend to enter, into contracts with government agencies, including the National Institute of Allergy and Infectious Diseases, a component of the National Institutes of Health. We also have established collaborations with and, in some instances, received funding from major medical and disease associations, including CHDI Foundation, Inc. Finally, to further enable the field and monetize our intellectual property rights, we also grant licenses to biotechnology companies for the development and commercialization of RNAi therapeutics for specified targets in which we have no direct strategic interest under our InterfeRx program, and to research companies that commercialize RNAi reagents or services under our research product licenses.

We also seek to form or advance new ventures and opportunities in areas outside our primary focus on RNAi therapeutics. Through an internal effort we refer to as Alnylam Biotherapeutics, we are advancing the application of RNAi technology to improve the manufacturing processes for biologics, including recombinant proteins and monoclonal antibodies. We have formed, and intend to form additional, collaborations through this effort with third-party biopharmaceutical companies. In addition, we recently announced our progress on VaxiRNA , an RNAi technology developed under our Alnylam Biotherapeutics initiative, for the enhanced production of viruses used in the manufacture of vaccine products. In October 2011, we entered into a VaxiRNA collaboration with GlaxoSmithKline, or GSK, for influenza vaccine production. Additionally, in 2007, we and Isis established Regulus Therapeutics Inc., or Regulus, a company focused on the discovery, development and commercialization of microRNA therapeutics. Regulus has formed collaborations with GSK and Sanofi to advance its efforts. Given the broad applications for RNAi technology, in addition to our efforts on Alnylam Biotherapeutics, VaxiRNA and Regulus, we believe new ventures and opportunities will be available to us.

Table of Contents

## Company information

We are a Delaware corporation. Our principal executive offices are located at 300 Third Street, Cambridge, Massachusetts 02142, and our telephone number at that address is (617) 551-8200. Our website address is *www.alnylam.com*. The information contained on our website is not incorporated by reference and should not be considered part of this prospectus supplement. We have included our website address in this prospectus supplement as an inactive textual reference only.

Table of Contents

# The offering

| | |
|---|---|
| **Common stock offered** | 7,000,000 shares |
| **Common stock to be outstanding after this offering** | 50,208,456 shares |
| **Option to purchase additional shares offered to the underwriter** | The underwriter has an option to purchase a maximum of 1,050,000 additional shares from us solely to cover over-allotments, if any. The underwriter can exercise this option at any time within 30 days from the date of this prospectus supplement. |
| **Use of Proceeds** | We estimate that the estimated net proceeds from this offering will be approximately $79.7 million, based on an assumed public offering price of $12.15 per share, the last reported sale price of our common stock on the NASDAQ Global Market on February 10, 2012, after deducting estimated discounts and commissions of 6% and estimated offering expenses payable by us. We intend to use the net proceeds from this offering for general corporate purposes, including research and development expenses, including clinical trial costs, working capital, capital expenditures and general and administrative expenses. See Use of Proceeds. |
| **Risk Factors** | You should read the Risk Factors section of this prospectus supplement beginning on page S-8 for a discussion of factors to consider before deciding to purchase shares of our common stock. |
| **NASDAQ Global Market symbol** | ALNY |

The number of shares of our common stock to be outstanding after this offering is based on 43,208,456 shares outstanding as of January 31, 2012, and excludes:

- 9,691,684 shares of common stock issuable upon the exercise of outstanding stock options at a weighted-average exercise price of $15.54 per share; and
- an aggregate of 664,062 additional shares of common stock reserved for future issuance under our 2009 stock incentive plan, our 2004 stock incentive plan and our 2004 employee stock purchase plan.

Except as otherwise noted, we have presented the information in this prospectus supplement assuming no exercise by the underwriter of the option to purchase up to 1,050,000 additional shares of our common stock in this offering.

In accordance with the terms of our investor rights agreement with Novartis in connection with this offering, Novartis has the right to purchase from us up to a number of shares such that its ownership after the offering remains at approximately 13.1% of the shares outstanding.

**Table of Contents**

Assuming the number of shares offered by us, as set forth in on the cover page of this prospectus supplement does not change, Novartis has the right to purchase up to 1,042,938 shares of our common stock and, if the option granted by us to the underwriter to purchase up to 1,050,000 additional shares is exercised in full, up to an additional 156,440 shares of our common stock, at a purchase price equal to the price that we sell shares in this offering if Novartis exercises this purchase right during the 30-day period after this offering. If Novartis exercises its purchase right after this 30-day period, it may purchase the shares at a purchase price that is a 10% premium to the price that we sell shares in this offering or a 10% premium to the market price at the time of purchase, whichever is greater. The number of shares of our common stock to be outstanding after this offering excludes all of the shares that Novartis will have the right to purchase from us. We cannot provide any assurance as to the exact number of shares of our common stock that Novartis will purchase, if any, in connection with this offering.

Table of Contents

# Risk factors

Investing in our common stock involves significant risks. In deciding whether to invest, you should carefully consider the following risk factors, as well as the other information contained in this prospectus supplement, the accompanying prospectus and in our filings with the Securities and Exchange Commission, or the SEC, that we have incorporated by reference in this prospectus supplement and the accompanying prospectus. Any of the following risks could have a material adverse effect on our business, financial condition, results of operations and prospects and cause the value of our stock to decline, which could cause you to lose all or part of your investment. The risks and uncertainties we have described are not the only ones facing our company. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our business operations.

## Risks related to our business

## Risks related to being an early stage company

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

As an early-stage development 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 tissues and cells;
- build and maintain a strong intellectual property portfolio;
- gain regulatory acceptance for the development of our product candidates and market success for any products we commercialize;
- develop and maintain successful strategic alliances; and
- manage our spending as costs and expenses increase due to clinical trials, regulatory approvals and commercialization.

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

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

We have concentrated our efforts and therapeutic product research on RNAi technology, and our future success depends on the successful development of this technology and products based on it. Neither we nor any other company has received regulatory approval to market therapeutics utilizing siRNAs, the class of molecule we are trying to develop into drugs. The scientific discoveries that form the basis for our efforts to discover and develop new drugs are relatively new. The scientific evidence to support the feasibility of developing drugs based on these

Table of Contents

discoveries is both preliminary and limited. Skepticism as to the feasibility of developing RNAi therapeutics has been expressed in scientific literature. For example, there are potential challenges to achieving safe RNAi therapeutics based on the so-called off-target effects and activation of the interferon response. In addition, decisions by other companies with respect to their RNAi development efforts may increase skepticism in the marketplace regarding the potential for RNAi therapeutics.

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

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

## Risks related to our financial results and need for financing

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

We have experienced significant operating losses since our inception. At December 31, 2011, we had an accumulated deficit of $401.0 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 revenues 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 anticipate that revenues derived from such sources will not be sufficient to make us consistently profitable.

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

Table of Contents

common stock could decline. In addition, we may be unable to raise capital, expand our business, develop additional product candidates or continue our operations.

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

We have used substantial funds to develop our RNAi technologies and will require substantial funds to conduct further research and development, including pre-clinical testing and clinical trials of our product candidates, and to manufacture and market any products that are approved for commercial sale. Because we cannot be certain of the length of time or activities associated with successful development of our product candidates, we are unable to estimate the actual funds we will require to develop and commercialize them.

Our future capital requirements and the period for which we expect our existing resources to support our operations may vary from what we expect. We have based our expectations on a number of factors, many of which are difficult to predict or are outside of our control, including:

- our progress in demonstrating that siRNAs can be active as drugs;
- our ability to develop relatively standard procedures for selecting and modifying siRNA product candidates;
- progress in our research and development programs, as well as the magnitude of these programs;
- the timing, receipt and amount of milestone and other payments, if any, from present and future collaborators, if any;
- the timing, receipt and amount of funding under current and future government or foundation contracts, if any;
- our ability to maintain and establish additional collaborative arrangements and/or new business initiatives;
- the resources, time and costs required to initiate and complete our pre-clinical and clinical trials, obtain regulatory approvals, and obtain and maintain licenses to third-party intellectual property;
- our ability to manufacture, or contract with third-parties for the manufacture of, our product candidates for clinical testing and commercial sale;
- the resources, time and cost required for the preparation, filing, prosecution, maintenance and enforcement of patent claims;
- our ability to achieve the anticipated cost reductions as a result of, and to successfully manage the potential impact of, our January 2012 strategic corporate restructuring and workforce reduction on our culture, collaborative relationships and business operations;
- the costs associated with legal activities, including litigation, arising in the course of our business activities and our ability to prevail in any such legal disputes;

progress in the research and development programs of Regulus; and

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

Table of Contents

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

Even if our estimates are correct, we will be required to seek additional funding in the future and intend to do so through either collaborative arrangements, public or private equity offerings or debt financings, or a combination of one or more of these funding sources. Additional funds may not be available to us on acceptable terms or at all.

In addition, the terms of any financing may adversely affect the holdings or the rights of our stockholders. For example, if we raise additional funds by issuing equity securities, under our shelf registration statement or otherwise, further dilution to our stockholders will result. In addition, as a condition to providing additional funds to us, future investors may demand, and may be granted, rights superior to those of existing stockholders. Moreover, our investor rights agreement with Novartis provides Novartis with the right generally to maintain its ownership percentage in us, subject to certain exceptions. These rights continue until the earlier of any sale by Novartis of shares of our common stock and the expiration or termination of our license agreement with Novartis, subject to certain exceptions. Pursuant to the terms of its investor rights agreement with us, over the past five years, Novartis purchased an aggregate of 335,033 shares of our common stock, resulting in aggregate payments to us of $7.6 million. At December 31, 2011, Novartis held 13.1% of our outstanding common stock. While the exercise of these rights by Novartis has provided us with funding, and the exercise in the future by Novartis may provide us with additional funding under some circumstances, these exercises have caused, and any future exercise of these rights by Novartis will also cause further, dilution to our stockholders. Debt financing, if available, may involve restrictive covenants that could limit our flexibility in conducting future business activities and, in the event of insolvency, would be paid before holders of equity securities received any distribution of corporate assets.

If we are unable to obtain funding on a timely basis, we may be required to significantly delay or curtail one or more of our research or development programs or undergo additional reductions in our workforce or other corporate restructuring activities. We also could be required to seek funds through arrangements with collaborators or others that may require us to relinquish rights to some of our technologies, product candidates or products that we would otherwise pursue on our own.

***If the estimates we make, or the assumptions on which we rely, in preparing our 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 is subject to risks which may cause losses and affect the liquidity of these investments.***

At December 31, 2011, we had $260.8 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 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. The market risks associated with our investment portfolio may have an adverse effect on our results of operations, liquidity and financial condition.

## Risks related to our dependence on third parties

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

In July 2007, we entered into a license and collaboration agreement with Roche. Under the license and collaboration agreement we granted Roche a non-exclusive license to our intellectual property to develop and commercialize therapeutic products that function through RNAi, subject to our existing contractual obligations to third parties. In November 2010, Roche announced the discontinuation of certain activities in research and early development, including their RNAi research efforts. In October 2011, Arrowhead announced its acquisition of RNA therapeutics assets from Roche, including our license and collaboration agreement with Roche. As a result of the assignment, Arrowhead now has all of the rights and obligations of Roche under that agreement. The license is limited to four therapeutic areas and may be expanded to include additional therapeutic areas, upon payment to us by Arrowhead of 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 Arrowhead, its affiliates, or sublicensees under the collaboration agreement, we are entitled to receive milestone payments upon achievement of specified development and sales events, totaling up to an aggregate of $100.0 million per therapeutic target, together with royalty payments based on worldwide annual net sales, if any. Our receipt of milestone payments under this agreement is dependent upon Arrowhead s ability to successfully develop and commercialize RNAi therapeutic products.

In May 2008, we entered into a similar license and collaboration agreement with Takeda, which is limited to two therapeutic areas, and which may be expanded to include additional therapeutic areas, upon payment to us by Takeda of an additional $50.0 million for each additional therapeutic area, if any. For each RNAi therapeutic product developed by Takeda, its affiliates and sublicensees, we are entitled to receive specified development and commercialization milestones, totaling up to $171.0 million per product, together with royalty payments based on worldwide annual net sales, if any. In addition, we agreed that we will not grant any other party rights to develop RNAi therapeutics in the Asian territory through May 2013.

Table of Contents

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

If Takeda, Novartis or Arrowhead fails to successfully develop products using our technology, we may not receive any milestone or royalty payments under our agreements with them. In addition, even if Takeda is not successful in its efforts, we are limited in our ability to form alliances with other parties in the Asian territory until May 2013. 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, Takeda could become a competitor of ours in the development of RNAi-based drugs targeting the same diseases that we choose to target. Takeda has significantly greater financial resources than we do and far more experience in developing and marketing drugs, which could put us at a competitive disadvantage if we were to compete with them in the development of RNAi-based drugs targeting the same disease.

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

We do not have any capability for sales, marketing or distribution and have limited capabilities for drug development. 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 such alliances in the future. For example, we intend to enter into worldwide or specific geographic collaborations relating to (1) RNAi platform and/or multi-target discovery alliances, and (2) select RNAi therapeutic programs in our pipeline, including ALN-PCS, ALN-HPN, ALN-TMP and ALN-VSP. In such alliances, we expect our current, and may expect our future, 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 agreements with the Massachusetts Institute of Technology, or MIT, Tekmira Pharmaceuticals Corporation, or Tekmira, The University of British Columbia, or UBC, and AlCana Technologies, Inc., or AlCana, and Arrowhead, among others, we have access to certain existing delivery technologies and/or are developing additional delivery capabilities. In addition, 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/or sell certain of our product candidates. We may have limited or no control over the development, sales, marketing and distribution activities of these third parties. Our future revenues may

Table of Contents

depend heavily on the success of the efforts of these third parties. For example, we will rely entirely on Kyowa Hakko Kirin for development and commercialization of any RNAi products for the treatment of RSV in Asia. If Kyowa Hakko Kirin is not successful in its commercialization efforts, our future revenues from RNAi therapeutics for the treatment of RSV may be adversely affected.

We may not be successful in entering into such alliances on terms favorable to us due to various factors, including our ability to successfully demonstrate proof of concept for our technology in man, our ability to demonstrate the safety and efficacy of our specific drug candidates, our ability to manufacture or have manufactured RNAi therapeutics, the strength of our intellectual property and/or concerns around challenges to our intellectual property. Even if we do succeed in securing any such alliances, we may not be able to maintain them if, for example, development or approval of a product candidate is delayed, challenges are raised as to the validity or scope of our intellectual property or sales of an approved drug are lower than we expected.

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

For certain product candidates that we may develop, we have formed collaborations to fund all or part of the costs of drug development and commercialization, such as our collaborations with Takeda, Cubist and Medtronic. We may not, however, be able to enter into additional collaborations for ALN-PCS, ALN-HPN, ALN-TMP or ALN-VSP, and the terms of any collaboration agreement we do secure may not be favorable to us. If we are not successful in our efforts to enter into future collaboration arrangements with respect to one or more of these product candidates, we may not have sufficient funds to develop that or any other product candidate internally, or to bring any product candidates to market. If we do not have sufficient funds to develop and bring our product candidates to market, we will not be able to generate 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.

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.

Table of Contents

In addition, if we have a dispute with a collaborator over the ownership of technology or other matters, or if a collaborator terminates its collaboration with us, for breach or otherwise, or determines not to pursue the research and development of RNAi therapeutics, it could delay our development of product candidates, result in the need for additional company resources to develop product candidates, make it more difficult for us to attract new collaborators and could adversely affect how we are perceived in the business and financial communities.

For example, in March 2011, Tekmira filed a civil complaint against us claiming misappropriation of its confidential and proprietary information and trade secrets, civil conspiracy and tortious interference with contractual relationships, unjust enrichment, contractual breach, breach of the implied covenant of good faith and fair dealing, unfair competition, false advertising, and unfair and deceptive trade practices by us. As a result of the litigation, we have been required to expend additional resources and management attention that would otherwise be engaged in other activities. Moreover, a collaborator, or in the event of a change in control of a collaborator or the assignment of a collaboration agreement to a third-party, the successor entity or assignee, could determine that it is in its interests to:

- pursue alternative technologies or develop alternative products, either on its own or jointly with others, that may be competitive with the products on which it is collaborating with us or which could affect its commitment to the collaboration with us;
- pursue higher-priority programs or change the focus of its development programs, which could affect the collaborator s commitment to us; or
- if it has marketing rights, choose to devote fewer resources to the marketing of our product candidates, if any are approved for marketing, than it does for product candidates developed without us.

If any of these occur, the development and commercialization of one or more product candidates could be delayed, curtailed or terminated because we may not have sufficient financial resources or capabilities to continue such development and commercialization on our own.

***Regulus is important to our business. If Regulus does not successfully develop drugs pursuant to our license and collaboration agreement, our business could be adversely affected. In addition, disagreements between us and Isis regarding the development of microRNA technology may cause significant delays and other impediments in the development of this technology, which could negatively affect the value of the technology and our investment in Regulus.***

In September 2007, we and Isis formed Regulus, of which we owned approximately 45% at December 31, 2011, to discover, develop and commercialize microRNA therapeutics. Regulus is exploring therapeutic opportunities that arise from dysregulation of microRNAs. Neither Regulus nor any other company has received regulatory approval to market therapeutics utilizing microRNA technology. In connection with the establishment of Regulus, we exclusively licensed to Regulus our intellectual property rights covering microRNA technology. Generally, we do not have rights to pursue microRNA therapeutics independently of Regulus. If Regulus is unable to discover, develop and commercialize microRNA therapeutics, our business could be adversely affected.

In April 2008, Regulus formed a collaboration with GSK pursuant to which GSK provided Regulus with a loan for $5.0 million, plus interest. In February 2010, Regulus formed an additional collaboration with GSK pursuant to which GSK provided Regulus with an additional $5.0 million loan, plus interest. These loans are guaranteed equally by us and Isis. If Regulus is unable to

Table of Contents

repay GSK or convert the loans into Regulus common stock, we could be liable for our share of these obligations, and our business could be adversely affected. In addition, Regulus operates as an independent company, governed by a board of directors. We and Isis each can elect an equal number of directors to serve on the Regulus board. Regulus researches and develops microRNA projects and programs pursuant to an operating plan that is approved by its board. Any disagreements between Isis and us regarding a development decision or any other decision submitted to Regulus board may cause significant delays in the development and commercialization of microRNA technology and could negatively affect the value of our investment in Regulus.

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

***We have very limited manufacturing experience or resources and we must incur significant costs to develop this expertise 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-current good manufacturing practice, or cGMP, material for use in *in vitro* and *in vivo* experiments. Some of our product candidates utilize specialized formulations, such as liposomes or lipid nanoparticles, 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 a limited number of third parties, who might not be able to deliver in a timely manner, or at all. In order to develop products, apply for regulatory approvals and commercialize our products, we will need to develop, contract for, or otherwise arrange for the necessary manufacturing capabilities. We may manufacture clinical trial materials ourselves or we may rely on others to manufacture the materials we will require for any clinical trials that we initiate. There are a limited number of manufacturers that supply synthetic siRNAs. We currently rely on several contract manufacturers for our supply of synthetic siRNAs. There are risks inherent in pharmaceutical manufacturing that could affect the ability of our contract manufacturers to meet our delivery time requirements or provide adequate amounts of material to meet our needs. Included in these risks are synthesis and purification failures and contamination during the manufacturing process, which could result in unusable product and cause delays in our development process, as well as additional expense to us. To fulfill our siRNA requirements, we may also need to secure alternative suppliers of synthetic siRNAs.

In addition to the manufacture of the synthetic siRNAs, we may have additional manufacturing requirements related to the technology required to deliver the siRNA to the relevant cell or tissue type, such as LNPs or conjugates. In some cases, the delivery technology we utilize is highly

Table of Contents

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. For example, under our agreements with Tekmira, we are obligated, subject to certain exceptions specified in our contract with Tekmira, 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. Failure by manufacturers to properly formulate our siRNAs for delivery could result in unusable product. Furthermore, a breach by such manufacturers of their contractual obligations or a dispute with such manufacturers would cause delays in our discovery and development process, as well as additional expense to us. Given the limited number of suppliers for our delivery technology and other materials, in the future, we expect to develop our own capabilities to manufacture drug substance, including siRNAs and siRNA conjugates, and/or finished drug product, including LNP formulations, as permitted under our manufacturing agreement with Tekmira, for human clinical use. If we develop these manufacturing capabilities by building our own manufacturing facility, it will require substantial expenditures. Also, we will likely need to hire and train employees to staff a new facility.

The manufacturing process for any products that we may develop is subject to the United States Food and Drug Administration, or 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 have existing, or enter into future, manufacturing arrangements with third parties, we depend, and will depend in the future, on these third parties to perform their obligations in a timely manner and consistent with contractual and regulatory requirements, including those related to quality control and quality assurance. The failure of a third-party manufacturer to perform its obligations as expected, or, if we elect to manufacture all or a portion of our product candidates ourselves, our failure to execute on our manufacturing requirements could adversely affect our business in a number of ways, including:

- we or our current or future collaborators may not be able to initiate or continue clinical trials of products that are under development;
- we or our current or future collaborators may be delayed in submitting regulatory applications, or receiving regulatory approvals, for our product candidates;
- we may lose the cooperation of our collaborators;
- our products could be the subject of inspections by regulatory authorities;
- we may be required to cease distribution or recall some or all batches of our products; and
- ultimately, we may not be able to meet commercial demands for our products.

If any third-party manufacturer with whom we contract fails to perform its obligations, we may be forced to manufacture the materials ourselves, for which we may not have the capabilities or resources, or enter into an agreement with a different third-party manufacturer, which we may not be able to do on reasonable terms, if at all. In some cases, the technical skills required to manufacture our products or product candidates may be unique or proprietary to the original

Table of Contents

manufacturer and we may have difficulty, or there may be contractual restrictions prohibiting us from, transferring such skills to a back-up or alternate supplier, or we may be unable to transfer such skills at all. In addition, if we are required to change manufacturers for any reason, we will be required to verify that the new manufacturer maintains facilities and procedures that comply with quality standards and with all applicable regulations and guidelines. The delays associated with the verification of a new manufacturer could negatively affect our ability to develop product candidates in a timely manner or within budget. Furthermore, a manufacturer may possess technology related to the manufacture of our product candidate that such manufacturer owns independently. This would increase our reliance on such manufacturer or require us to obtain a license from such manufacturer in order to have another third-party manufacture our products or product candidates.

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

We have no sales, marketing or distribution experience. We currently expect to rely heavily on third parties to launch and market certain of our product candidates, if approved. However, if we elect to develop internal sales, distribution and marketing capabilities as part of our core product strategy, we will need to invest significant financial and management resources. For core 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 core 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, particularly given our recent workforce reduction, our ability to implement our business plan may be adversely affected.***

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

Table of Contents

We 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. In addition, as a result of our September 2010 and January 2012 corporate restructurings and workforce reductions, we may face additional challenges in retaining our existing employees and recruiting new employees to join our company as our business needs change. 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 future business plan.

***Our corporate restructuring and workforce reduction plan may not result in anticipated savings, could result in total costs and expenses that are greater than expected and could disrupt our business.***

In January 2012, we announced a corporate restructuring and workforce reduction plan pursuant to which we intend to reduce our workforce by approximately 33%. We are taking these actions in order to reduce costs, streamline operations and improve our cost structure, and we expect that this restructuring plan will result in significant savings in 2012 operating expenses. The workforce reduction is expected to be substantially completed by the end of the first quarter of 2012.

As a result of the reduction in workforce, we expect to record restructuring charges and make future payments of approximately $4.0 million, a substantial portion of which we anticipate will be recorded in the first quarter of 2012. These estimated restructuring charges are based on a number of assumptions. Actual results may differ materially and additional charges not currently expected may be incurred in connection with, or as a result of, these reductions. In addition, we may not realize, in full or in part, the anticipated benefits, savings and improvements in our cost structure from our restructuring efforts due to unforeseen difficulties, delays or unexpected costs. If we are unable to achieve the anticipated benefits, savings or improvements in our cost structure in the expected time frame or other unforeseen events occur, our business and results of operations may be adversely affected.

Our restructuring plan may be disruptive to our operations. For example, cost savings measures may distract management from our core business, harm our reputation, yield unanticipated consequences, such as attrition beyond planned reductions in workforce, or increased difficulties in our day-to-day operations, and may adversely affect employee morale. Our workforce reductions could also harm our ability to attract and retain qualified management, scientific, manufacturing and sales and marketing personnel who are critical to our business. Any failure to attract or retain qualified personnel could prevent us from successfully developing and commercializing our products and product candidates in the future.

***We may have difficulty 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.***

Despite our recent workforce reduction in connection with our strategic corporate restructuring, we expect that as we seek to increase the number of product candidates we are developing we will need to expand our operations in the future. This 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 due to our development progress, we expect

Table of Contents

that we will need to manage additional relationships with various collaborators, suppliers and other organizations. Our ability to manage our operations and future growth will require us to continue to improve our operational, financial and management controls, 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.***

Before obtaining regulatory approval for the commercial distribution of our product candidates, we must conduct, at our own expense, extensive pre-clinical tests and clinical trials to demonstrate the safety and efficacy in humans of our product candidates. Pre-clinical and clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome, and the historical failure rate for product candidates is high. We currently have several programs in clinical development. We are developing ALN-RSV01 for the treatment of 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 clinical trial is to repeat and extend the clinical results observed in a Phase IIa clinical trial. In addition, in August 2011, we completed a Phase I clinical trial for ALN-VSP, our first systemically delivered RNAi therapeutic. We are developing ALN-VSP for the treatment of primary and secondary liver cancer. In July 2010, we also initiated a Phase I clinical trial for ALN-TTR01, our second systemically delivered RNAi therapeutic, which targets the transthyretin, or TTR, gene for the treatment of ATTR. In September 2011, we initiated a Phase I clinical trial for ALN-PCS for the treatment of severe hypercholesteremia. ALN-PCS is formulated in a proprietary second-generation LNP formulation. However, we may not be able to further advance these or any other product candidate through clinical trials.

If we enter into clinical trials, the results from pre-clinical testing or early clinical trials of a product candidate may not predict the results that will be obtained in subsequent human clinical trials of that product candidate or any other product candidate. For example, ALN-RSV01 may not demonstrate the same results in the Phase IIb clinical trial as it did in our Phase IIa clinical trial. In addition, ALN-VSP, ALN-TTR01 and ALN-PCS employ novel delivery formulations that have yet to be extensively evaluated in human clinical trials and proven safe and effective. We, the

Table of Contents

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

Clinical trials of a new product candidate require the enrollment of a sufficient number of patients, including patients who are suffering from the disease the product candidate is intended to treat and who meet other eligibility criteria. Rates of patient enrollment are affected by many factors, including the size of the patient population, the age and condition of the patients, the stage and severity of disease, the nature of the protocol, the proximity of patients to clinical sites, the availability of effective treatments for the relevant disease, the seasonality of infections and the eligibility criteria for the clinical trial. In our ALN-VSP clinical trial, one patient with advanced pancreatic neuroendocrine cancer with extensive involvement of the liver developed hepatic failure five days following the second dose of ALN-VSP and subsequently died; this was deemed possibly related to the study drug. Six additional patients treated at the same dose did not exhibit any evidence of hepatotoxicity. In August 2011, we announced the completion of the ALN-VSP clinical trial. In our ALN-PCS clinical trial, we reported preliminary safety data that a mild, transient rash was observed in five subjects, including two who received placebo. In addition, our ALN-TTR01 trial targets a small population of patients suffering from ATTR. Delays or difficulties in patient enrollment or difficulties retaining trial participants can result in increased costs, longer development times or termination of a clinical trial.

Clinical trials also require the review, oversight and approval of IRBs, which continually review clinical investigations and protect the rights and welfare of human subjects. Inability to obtain or delay in obtaining IRB approval can prevent or delay the initiation and completion of clinical trials, and the FDA or foreign regulatory authorities may decide not to consider any data or information derived from a clinical investigation not subject to initial and continuing IRB review and approval in support of a marketing application.

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

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

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

- delays in filing investigational new drug applications 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;

Table of Contents

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

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

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

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

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

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

greater than anticipated clinical trial costs;

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

poor effectiveness of our product candidates during clinical trials;

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

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

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

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

Even if we successfully complete clinical trials of our product candidates, any given product candidate may not prove to be a safe and effective treatment for the 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 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

Table of Contents

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 addition, the use of a specialized delivery system, even if previously approved, could complicate the design or analysis of clinical trials for our RNAi therapeutics. 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, unable to commercialize our product candidates.***

Our product candidates are subject to extensive governmental regulations relating to, among other things, research, testing, development, manufacturing, safety, efficacy, approval, recordkeeping, reporting, labeling, storage, 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.

Because the drugs we are developing may represent a new class of drug, the FDA and its foreign counterparts have not yet established any definitive policies, practices or guidelines in relation to these drugs. While we believe 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

Table of Contents

approved treatments for some of the diseases for which we may seek approval, in order to receive regulatory approval, we may need to demonstrate through clinical trials that the product candidates we develop to treat these diseases, if any, are not only safe and effective, but safer or more effective than existing products. Furthermore, in recent years, there has been increased public and political pressure on the FDA with respect to the approval process for new drugs, and the FDA s standards, especially regarding drug safety, appear to have become more stringent.

Any delay or failure in obtaining required approvals could have a material adverse effect on our ability to generate revenues from the particular product candidate for which we are seeking approval. Furthermore, any regulatory approval to market a product may be subject to limitations on the approved uses for which we may market the product or the labeling or other restrictions. In addition, the FDA has the authority to require a Risk Evaluation and Mitigation Strategy, or REMS, plan as part of an NDA or biologics license application, or BLA, or after approval, which may impose further requirements or restrictions on the distribution or use of an approved drug or biologic, such as limiting prescribing to certain physicians or medical centers that have undergone specialized training, limiting treatment to patients who meet certain safe-use criteria and requiring treated patients to enroll in a registry. These limitations and restrictions may limit the size of the market for the product and affect reimbursement by third-party payors.

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

***Even if we obtain regulatory approvals, our marketed drugs will be subject to ongoing regulatory review. If we fail to comply with continuing U.S. and foreign requirements, our approvals could be limited or withdrawn, we could be subject to other penalties, and our business would be seriously harmed.***

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

The FDA has significant post-market authority, including, for example, the authority to require labeling changes based on new safety information and to require post-market studies or clinical trials to evaluate serious safety risks related to the use of a drug and to require withdrawal of the product from the market. The FDA also has the authority to require a REMS plan after approval, which may impose further requirements or restrictions on the distribution or use of an approved drug.

Table of Contents

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 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, injunction, civil penalties and criminal prosecution.

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

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

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

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

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

relative convenience and ease of administration of our product candidates;

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

the success of our physician education programs;

the availability of adequate government and third-party payor coverage and 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.

Table of Contents

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

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

- the U.S. federal healthcare program anti-kickback law, which prohibits, among other things, persons from soliciting, receiving or providing remuneration, directly or indirectly, to induce either the referral of an individual for a healthcare item or service, or the purchasing or ordering of an item or service, for which payment may be made under a federal healthcare program such as Medicare or Medicaid;

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

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

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

If our operations are found to be in violation of any such requirements, we may be subject to penalties, including civil or criminal penalties, monetary damages, the curtailment or restructuring of our operations, loss of eligibility to obtain approvals from the FDA, or exclusion from participation in government contracting, healthcare reimbursement or other government programs, including Medicare and Medicaid, any of which could adversely 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:

- adverse regulatory inspection findings;

- warning letters;

Table of Contents

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 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.

Table of Contents

We currently expect that any drugs we develop may need to be administered under the supervision of a physician. Under currently applicable U.S. 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 healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement rates. Our inability to promptly obtain coverage and adequate reimbursement rates from both government-funded and private payors for new drugs that we develop and for which we obtain regulatory approval could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products, and our overall financial condition.

We believe that the efforts of governments and third-party payors to contain or reduce the cost of healthcare and legislative and regulatory proposals to broaden the availability of healthcare will continue to affect the business and financial condition of pharmaceutical and biopharmaceutical companies. A number of legislative and regulatory changes in the healthcare system in the United States and other major healthcare markets have been proposed in recent years, and such efforts have expanded substantially in recent years. These developments have included prescription drug benefit legislation that was enacted and took effect in January 2006, healthcare reform legislation enacted by certain states, and major healthcare reform legislation that was passed by Congress and enacted into law in the United States in 2010. These developments could, directly or indirectly, affect our ability to sell our products, if approved, at a favorable price.

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

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

Table of Contents

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

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

Pharmaceutical companies are required to pay an annual non-tax deductible fee to the federal government based on each company s market share of prior year total sales of branded products to certain federal healthcare programs, such as Medicare, Medicaid, Department of Veterans Affairs and Department of Defense. Since we expect our branded pharmaceutical sales to constitute a small portion of the total federal health program pharmaceutical market, we do not expect this annual assessment to have a material impact on our financial condition.

The new law provides that approval of an application for a follow-on biologic product may not become effective until 12 years after the date on which the prior innovator biologic product was first licensed by the FDA, with a possible six-month extension for pediatric products. After this exclusivity ends, it will be easier for generic manufacturers to enter the market, which is likely to reduce the pricing for such products and could affect the company s profitability.

The full effects of the U.S. healthcare reform legislation cannot be known until the new law is implemented through regulations or guidance issued by the Centers for Medicare & Medicaid Services and other federal and state healthcare agencies. The financial impact of the U.S. healthcare reform legislation over the next few years will depend on a number of factors, including but not limited, to the policies reflected in implementing regulations and guidance, and changes in sales volumes for products affected by the new system of rebates, discounts and fees. The new legislation may also have a positive impact on our future net sales, if any, by increasing the aggregate number of persons with healthcare coverage in the United States, but such increases are unlikely to be realized until approximately 2014 at the earliest.

Moreover, we cannot predict what healthcare reform initiatives may be adopted in the future. Further federal and state legislative and regulatory developments are likely, and we expect ongoing initiatives in the United States to increase pressure on drug pricing. Such reforms could have an adverse effect on anticipated revenues from product candidates that we may successfully develop and for which we may obtain regulatory approval and may affect our overall financial condition and ability to develop drug candidates.

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

Our business exposes us to significant potential product liability risks that are inherent in the development, testing, manufacturing and marketing of human therapeutic products. Product liability claims could delay or prevent completion of our clinical development programs. If we succeed in marketing products, such claims could result in an FDA investigation of the safety and effectiveness of our products, our manufacturing processes and facilities or our marketing programs, and potentially a recall of our products or more serious enforcement action, limitations on the approved indications for which they may be used, or suspension or withdrawal of approvals. Regardless of the merits or eventual outcome, liability claims may also result in 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

Table of Contents

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.

Table of Contents

Our strategy depends on our ability to rapidly identify and seek patent protection for our discoveries. In addition, we may rely on third-party collaborators to file patent applications relating to proprietary technology that we develop jointly during certain collaborations. The process of obtaining patent protection is expensive and time-consuming. If our present or future collaborators fail to file and prosecute all necessary and desirable patent applications at a reasonable cost and in a timely manner, our business will be adversely affected. Despite our efforts and the efforts of our collaborators to protect our proprietary rights, unauthorized parties may be able to obtain and use information that we regard as proprietary. While issued patents are presumed valid, this does not guarantee that the patent will survive a validity challenge or be held enforceable. Any patents we have obtained, or obtain in the future, may be challenged, invalidated, adjudged unenforceable or circumvented by parties attempting to design around our intellectual property. Moreover, third parties or the United States Patent and Trademark Office, or USPTO, may commence interference proceedings involving our patents or patent applications. For example, during 2011, the USPTO declared an interference between our issued patent covering ALN-VSP, our RNAi therapeutic undergoing clinical testing for the treatment of liver cancers, and a pending third-party application assigned to Protiva Biotherapeutics Inc., or Protiva (which was acquired by Tekmira in 2008), the effect of which called into question the validity and/or enforceability of our patent. The interference proceedings are ongoing. If Protiva is successful in obtaining a dominating claim, we would require a license to Protiva s patent to commercialize ALN-VSP in the United States. Any challenge to, finding of unenforceability or invalidation or circumvention of, our patents or patent applications, would be costly, would require significant time and attention of our management and could have a material adverse effect on our business.

Our pending patent applications may not result in issued patents. The patent position of pharmaceutical or biotechnology companies, including ours, is generally uncertain and involves complex legal and factual considerations. The standards that the USPTO and its foreign counterparts use to grant patents are not always applied predictably or uniformly and can change. Similarly, the ultimate degree of protection that will be afforded to biotechnology inventions, including ours, in the United States and foreign countries, remains uncertain and is dependent upon the scope of the protection decided upon by patent offices, courts and lawmakers. Moreover, there are periodic discussions in the Congress of the United States and in international jurisdictions about modifying various aspects of patent law. For example, the America Invents Act was recently enacted into law and includes a number of changes to the patent laws of the United States. If any changes to the patent laws 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

Table of Contents

others, Cancer Research Technology Limited, Isis, MIT, Whitehead Institute for Biomedical Research, or Whitehead, Max Planck Innovation GmbH, or Max Planck Innovation, Tekmira, The University of Texas Southwest Medical Center and Arrowhead. We also intend to enter into additional licenses to third-party intellectual property in the future.

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

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

RNAi is a relatively new scientific field, the commercial exploitation of which has resulted in many different patents and patent applications from organizations and individuals seeking to obtain patent protection in the field. We have obtained grants and issuances of RNAi patents and have licensed many of these patents from third parties on an exclusive basis. The issued patents and pending patent applications in the United States and in key markets around the world that we own or license claim many different methods, compositions and processes relating to the discovery, development, manufacture and commercialization of RNAi therapeutics.

Specifically, we have a portfolio of patents, patent applications and other intellectual property covering: fundamental aspects of the structure and uses of siRNAs, including their manufacture and use as therapeutics, and RNAi-related mechanisms; chemical modifications to siRNAs that improve their suitability for therapeutic uses; siRNAs directed to specific targets as treatments for particular diseases; and delivery technologies, such as in the field of cationic liposomes.

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

rights could be costly to us, could require significant time and attention of our management and could have a material adverse effect on our business and our ability to successfully compete in the field of RNAi.

There are many issued and pending patents that claim aspects of oligonucleotide chemistry that we may need to apply to our siRNA therapeutic candidates. There are also many issued patents that claim targeting genes or portions of genes that may be relevant for siRNA drugs we wish to develop. Thus, it is possible that one or more organizations will hold patent rights to which we will need a license. If those organizations refuse to grant us a license to such patent rights on reasonable terms, we may not be able to market products or perform research and development or other activities covered by these patents.

***If we become involved in patent litigation or other proceedings related to a determination of rights, we could incur substantial costs and expenses, substantial liability for damages or be required to stop our product development and commercialization efforts.***

Third parties may sue us for infringing their patent rights. Likewise, we may need to resort to litigation to enforce a patent issued or licensed to us or to determine the scope and validity of proprietary rights of others. For example, on January 17, 2012, we filed a complaint in the U.S. District Court for the District of Massachusetts against Tekmira for patent infringement arising from Tekmira s research activities providing LNP-formulated siRNA molecules to a pharmaceutical collaborator. As alleged in the complaint, we do not believe Tekmira s activities are protected under the exemption from patent infringement for drug development. Pursuant to the complaint, we believe Tekmira has infringed a number of issued patents related to siRNA and LNP technologies, including: U.S. Patent No. 7,695,902; U.S. Patent No. 6,858,225; U.S. Patent No. 6,815,432; U.S. Patent No. 6,534,484; U.S. Patent No. 6,586,410; and U.S. Patent No. 6,858,224. Under our contractual right to enforce U.S. Patent No. 7,695,902 owned by Isis, we joined Isis to the suit as a co-plaintiff. We and Isis are seeking judgment that Tekmira has infringed the patents at issue, a permanent injunction enjoining the infringing activities, damages, and costs and expenses, including attorneys fees.

In addition, a third party may claim that we have improperly obtained or used its confidential or proprietary information. For example, in March 2011, Tekmira and Protiva filed a civil complaint against us in the Business Litigation Section of the Suffolk County Superior Court, in Boston, Massachusetts, and in June 2011, the plaintiffs filed an amended complaint adding AlCana, a research collaborator of ours, as a defendant. The amended complaint alleges misappropriation of the plaintiffs confidential and proprietary information and trade secrets, civil conspiracy and tortious interference with contractual relationships by us and AlCana, and unjust enrichment, contractual breach, breach of the implied covenant of good faith and fair dealing, unfair competition, false advertising, unfair and deceptive trade practices by us. The plaintiffs seek, among other relief, injunctive relief, unspecified compensatory and punitive damages, attorneys fees, the termination of licenses that the plaintiffs provided to us and the relinquishment and transfer of certain of our intellectual property rights, including patents covering our MC3 technology. In April 2011, we served and filed an answer to the plaintiffs original complaint denying the plaintiffs claims and asserted counterclaims against the plaintiffs. In June 2011, we served and filed an answer to the plaintiffs amended complaint denying the plaintiffs claims and asserted counterclaims against the plaintiffs for breach of contract, defamation, breach of covenant not to sue, breach of patent prosecution and non-use provisions, misappropriation of confidential and proprietary information and trade secrets, unjust enrichment, breach of the implied covenant of good faith and fair dealing, as well as violations of Massachusetts statutes. We are seeking monetary damages, attorneys fees and equitable relief on our counterclaims. In

Table of Contents

September 2011, the Court granted the plaintiffs motion to dismiss our counterclaim for defamation. The plaintiffs did not move to dismiss any of our other counterclaims, all of which remain pending. The case is currently in discovery and we expect a trial to start in October 2012. We intend to vigorously defend ourselves in this matter. However, litigation is subject to inherent uncertainty and this matter could ultimately be decided against us and we could be required to pay substantial damages. We have also incurred, and will continue to incur during the pendency of the litigation, significant costs, and the defense of this litigation has diverted, and until resolved will continue to divert, the attention of our management and other resources that would otherwise be engaged in other activities.

Furthermore, third parties may challenge the inventorship of our patents or licensed patents. For example, in March 2011, the University of Utah, or Utah, filed a complaint in the United States District Court for the District of Massachusetts against us, Max Planck Gesellschaft Zur Forderung Der Wissenschaften E.V. and Max Planck Innovation, together, Max Planck, Whitehead, MIT and the University of Massachusetts, or UMass, claiming that a professor of Utah is the sole inventor, or in the alternative, a joint inventor of certain of our in-licensed patents. The original complaint was not served on any of the parties and, in July 2011, Utah filed an amended complaint containing substantially the same claims as the original complaint against us, Max Planck, Whitehead, MIT and UMass. The amended complaint alleges the defendants have incorrectly determined inventorship of some of our in-licensed patents and further claims unjust enrichment, unfair competition, false advertising and seeks correction of inventorship, injunctive relief and unspecified damages. In October 2011, we, Max Planck, Whitehead, MIT and UMass filed a motion to dismiss and UMass filed a motion to dismiss on separate grounds, which we, Max Planck, Whitehead and MIT have joined. In December 2011, Utah filed a second amended complaint dropping UMass as a defendant and adding as defendants several UMass officials. We intend to vigorously defend ourselves in this matter, however, litigation is subject to inherent uncertainty and a court could ultimately rule against us.

In addition, in connection with certain license and collaboration agreements, we have agreed to indemnify certain third parties for certain costs incurred in connection with litigation relating to intellectual property rights or the subject matter of the agreements. The cost to us of any litigation or other proceeding relating to intellectual property rights, even if resolved in our favor, could be substantial, and litigation would divert our management s efforts. Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. Uncertainties resulting from the initiation and continuation of any litigation could delay our research and development efforts and limit our ability to continue our operations.

If any parties successfully claim that our creation or use of proprietary technologies infringes upon or otherwise violates their intellectual property rights, we might be forced to pay damages, potentially including treble damages, if we are found to have willfully infringed on such parties patent rights. In addition to any damages we might have to pay, a court could require us to stop the infringing activity or obtain a license. Any license required under any patent may not be made available on commercially acceptable terms, if at all. In addition, such licenses are likely to be non-exclusive and, therefore, our competitors may have access to the same technology licensed to us. If we fail to obtain a required license and are unable to design around a patent, we may be unable to effectively market some of our technology and products, which could limit our ability to generate revenues or achieve profitability and possibly prevent us from generating revenue sufficient to sustain our operations. Moreover, we expect that a number of our collaborations will provide that royalties payable to us for licenses to our intellectual property may be offset by amounts paid by our collaborators to third parties who have competing or

Table of Contents

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 or other rights that are necessary for developing and protecting our RNAi technology and any related product candidates that we develop, or we could lose certain 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, patent prosecution and enforcement, 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. For example, in connection with its lawsuit against us, Tekmira has alleged that we breached our license agreements with it and Protiva and is seeking that the court terminate such license agreements. If this matter is decided in Tekmira s favor, we could lose access to certain aspects of our LNP delivery technology, including MC3, which would adversely impact certain of our clinical development programs, or be required to pay additional milestones and royalties to Tekmira. In addition, while we cannot currently determine the amount of the royalty obligations we will be required to pay on sales of future products, if any, the amounts may be significant. The amount of our future royalty obligations will depend on the technology and intellectual property we use in products that we successfully develop and commercialize, if any. Therefore, even if we successfully develop and commercialize products, we may be unable to achieve or maintain profitability.

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

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

## 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;

Table of Contents

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 ATTR, hemophilia, severe hypercholesterolemia, refractory anemia, hemoglobinopathies, including beta-thalassemia and sickle-cell anemia, RSV, liver cancers and HD, and have a number of additional discovery programs targeting other diseases. These drugs 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 recruit our employees, which could negatively impact our level of expertise and the ability to execute on our business plan. Furthermore, we also face competition from existing and new treatment methods that reduce or eliminate the need for drugs, such as the use of advanced medical devices. The development of new medical devices or other treatment methods for the diseases we are targeting could make our product candidates noncompetitive, obsolete or uneconomical.

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

In addition to the competition we face from competing drugs in general, we also face competition from other companies working to develop novel drugs using technology that competes more directly with our own. We are aware of multiple companies that are working in

Table of Contents

the field of RNAi. In addition, we granted licenses or options for licenses to Isis, GeneCare Research Institute Co., Ltd., Benitec Ltd., Arrowhead and its subsidiary, Calando Pharmaceuticals, Inc., Tekmira, Quark Pharmaceuticals, Inc., Sylentis S.A.U. and others under which these companies may independently develop RNAi therapeutics against a limited number of targets. Any of these companies may develop its RNAi technology more rapidly and more effectively than us. Merck & Co., Inc., or Merck, was one of our collaborators and a licensee under our intellectual property for specified disease targets until September 2007, at which time we and Merck agreed to terminate our collaboration. As a result of its acquisition of Sirna Therapeutics, Inc. in December 2006, and in light of the mutual termination of our collaboration, Merck, which has substantially more resources and experience in developing drugs than we do, may become a direct competitor.

In addition, as a result of agreements that we have entered into, Arrowhead, as the assignee of Roche, and Takeda have obtained non-exclusive licenses, and Novartis has obtained specific exclusive licenses for 31 gene targets, to certain aspects of our technology that give them the right to compete with us in certain circumstances We also compete with companies working to develop antisense-based drugs. Like RNAi therapeutics, antisense drugs target messenger RNAs, or 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.

Our Alnylam Biotherapeutics efforts will also face competition from established companies developing and commercializing technology applications to improve the manufacturing processes for drugs. If these companies advance and market their technologies more rapidly than Alnylam Biotherapeutics, we may be unable to establish collaborations for Alnylam Biotherapeutics with established biologic manufacturers, selling licenses, products and services.

## Risks related to this offering and our common stock

***Investors in this offering will pay a much higher price than the book value of our common stock.***

If you purchase common stock in this offering, you will incur an immediate and substantial dilution in net tangible book value of $8.18 per share, after giving effect to the sale by us of 7,000,000 shares of common stock offered in this offering at an assumed public offering price of $12.15 per share, the last reported sale price of our common stock on the NASDAQ Global Market on February 10, 2012, and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. In the past, we have issued options to acquire common stock at prices significantly below this offering price. To the extent these outstanding options are ultimately exercised, you will incur additional dilution. In addition, if the underwriter exercises its option to purchase additional shares or Novartis exercises its right to purchase additional shares, you will incur additional dilution.

Table of Contents

***Our management will have broad discretion over the use of the net proceeds from this offering, you may not agree with how we use the proceeds and the proceeds may not be invested successfully.***

Our management will have broad discretion as to the use of the net proceeds from any offering by us and could use them for purposes other than those contemplated at the time of this offering. Accordingly, you may be relying on the judgment of our management with regard to the use of these net proceeds, and you will not have the opportunity, as part of your investment decision, to assess whether the proceeds are being used appropriately. It is possible that the proceeds will be invested in a way that does not yield a favorable, or any, return for Alnylam.

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

The market price of our common stock has and may continue to fluctuate significantly in response to factors that are beyond our control. The stock market in general has recently experienced extreme price and volume fluctuations. The market prices of securities of pharmaceutical and biotechnology companies have been extremely volatile, and have experienced fluctuations that often have been unrelated or disproportionate to the operating performance of these companies. These broad market fluctuations could result in extreme fluctuations in the price of our common stock, which could cause purchasers of our common stock to incur substantial losses.

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

***Novartis ownership of our common stock could delay or prevent a change in corporate control.***

At December 31, 2011, Novartis held 13.1% of our outstanding common stock and has the right to maintain its ownership percentage until the earlier of any sale by Novartis of shares of our common stock and the expiration or termination of our collaboration and license agreement, subject to certain exceptions. This concentration of ownership may harm the market price of our common stock by:

delaying, deferring or preventing a change in control of our company;

impeding a merger, consolidation, takeover or other business combination involving our company; or

discouraging a potential acquirer from making a tender offer or otherwise attempting to obtain control of our company.

Table of Contents

***Sales of additional shares of our common stock could result in dilution to existing stockholders and cause the price of our common stock to decline.***

Sales of substantial amounts of our common stock in the public market, or the availability of such shares for sale, by us or others could adversely affect the price of our common stock. Novartis has rights, subject to certain conditions, to require us to file registration statements covering its shares or to include its shares in registration statements that we file. In addition, if Novartis decides to sell 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

# Special note regarding forward-looking statements

This prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. All statements, other than statements of historical facts, that we include in this prospectus supplement, the accompanying prospectus and in the documents incorporated by reference into this prospectus supplement and the accompanying prospectus may be deemed forward-looking statements for purposes of the Securities Act and the Exchange Act. We use words such as believe, expect, anticipate, may, could, intend, will, plan, target, goal anticipate, estimate, similar expressions to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These statements appear throughout this prospectus supplement, the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus and are statements regarding our current intent, belief or expectation, primarily with respect to our operations and related industry developments. Examples of these statements include, but are not limited to, statements regarding the following: our current and anticipated clinical trials; the progress of our research and development programs; our corporate collaborations, including potential future licensing fees and milestone and royalty payments; protection of our intellectual property; the outcome of litigation; the sufficiency of our cash resources; and our operations and legal risks. We cannot guarantee that we actually will achieve the plans, intentions or expectations disclosed in our forward-looking statements and, accordingly, you should not place undue reliance on our forward-looking statements. There are a number of important factors that could cause actual results or events to differ materially from those expressed or implied by these forward-looking statements, including those discussed under Risk Factors and elsewhere in this prospectus supplement.

Any forward-looking statement speaks only as of the date on which it is made, and we disclaim any obligation to update any forward-looking statement to reflect events or circumstances after the date on which the statement is made or to reflect the occurrence of unanticipated events. New factors emerge from time to time, and it is not possible for us to predict which factors will arise. In addition, we cannot assess the impact of each factor on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements.

Table of Contents

# Use of proceeds

We estimate that the net proceeds from the sale of 7,000,000 shares of our common stock that we are offering will be approximately $79.7 million, based on an assumed public offering price of $12.15 per share, the last reported sale price of our common stock on the NASDAQ Global Market on February 10, 2012, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us and assuming the underwriter does not exercise its option to purchase additional shares of common stock. A $0.25 increase (decrease) in the assumed public offering price per share of our common stock would increase (decrease) the estimated net proceeds that we receive from this offering by approximately $1.6 million, assuming that the number of shares offered by us, as set forth on the cover page of this prospectus, does not change.

We intend to use the net proceeds of this offering for general corporate purposes, ultimately focused on advancing our clinical pipeline. Although we have not yet identified specific uses for these proceeds, we currently anticipate using the proceeds for some or all of the following purposes:

- research and development expenses, including for the advancement of ALN-TTR02 for the treatment of ATTR through Phase III clinical trials, the advancement of ALN-APC for the treatment of hemophilia to human proof-of-concept data, and the advancement of additional Alnylam 5x15 programs into the clinic with existing partners and potential new alliances;
- working capital;
- capital expenditures; and
- general and administrative expenses.

We have not determined the amounts we plan to spend on any of the areas identified above or the timing of these expenditures. As a result, our management will have broad discretion to allocate the net proceeds from this offering. We may temporarily invest the net proceeds in investment-grade, interest-bearing securities until they are used for their stated purpose.

# Price range of common stock

Our common stock is listed on The NASDAQ Global Market and trades under the symbol ALNY . The following table sets forth, for the quarterly periods indicated, the high and low sale price per share of our common stock as reported on The NASDAQ Global Market:

| | High | Low |
|---|---|---|
| **2010** | | |
| First Quarter | $ 19.29 | $ 16.41 |
| Second Quarter | 17.59 | 14.88 |
| Third Quarter | 16.36 | 12.24 |
| Fourth Quarter | 13.98 | 8.79 |
| **2011** | | |
| First Quarter | $ 12.34 | $ 9.03 |
| Second Quarter | 10.59 | 8.80 |
| Third Quarter | 10.37 | 6.28 |
| Fourth Quarter | 8.62 | 5.88 |
| **2012** | | |
| First Quarter (through February 10, 2012) | $ 13.25 | $ 8.33 |

On February 10, 2012, the last reported sale price of our common stock was $12.15 per share.

# Dividend policy

We have never declared or paid any cash dividends on our common stock. We anticipate that, in the foreseeable future, we will continue to retain any earnings for use in the operation of our business and will not pay any cash dividends.

Table of Contents

# Dilution

If you purchase our common stock in this offering, your interest will be diluted to the extent of the difference between the public offering price per share and the net tangible book value per share of our common stock after this offering. We calculate net tangible book value per share by subtracting our total liabilities from our total tangible assets and dividing the difference by the number of outstanding shares of our common stock.

Our net tangible book value at December 31, 2011 was $117.7 million, or $2.76 per share, based on approximately 42.7 million shares of our common stock then outstanding. After giving effect to the sale by us of 7,000,000 shares of common stock in this offering at an assumed public offering price of $12.15 per share, the last sale price of our common stock on the NASDAQ Global Market on February 10, 2012, less the estimated underwriting discounts and commissions and estimated offering expenses payable by us, our net tangible book value at December 31, 2011 would be $197.4 million, or $3.97 per share. This represents an immediate increase in net tangible book value of $1.21 per share to existing stockholders and an immediate dilution of $8.18 per share to investors in this offering. The following table illustrates this per share dilution:

| | | |
|---|---|---|
| Assumed public offering price per share | | $ 12.15 |
| Net tangible book value per share as of December 31, 2011 | $ 2.76 | |
| Increase per share attributable to new investors purchasing shares in this offering | 1.21 | |
| Net tangible book value per share after this offering | 3.97 | |
| Dilution per share to new investors | | $ 8.18 |

A $0.25 increase (decrease) in the assumed public offering price per share of our common stock would increase (decrease) our net tangible book value after giving effect to this offering by approximately $1.4 million, the net tangible book value per share after giving effect to this offering by $0.03 and the dilution in net tangible book value per share to new investors after giving effect in this offering by $0.22, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

In the discussion and table above, we assume no exercise of outstanding options. As of January 31, 2012, there were 9,691,684 shares of common stock issuable upon exercise of outstanding options with a weighted average exercise price of $15.54 per share. To the extent that any of these outstanding options are exercised, there will be further dilution to new investors. In addition, in the discussion and table above, we assume no exercise by the underwriter of its overallotment option and no exercise by Novartis of its right to purchase shares in connection with this offering. If the underwriter exercises its overallotment option or Novartis purchases additional shares, there will be further dilution to new investors.

Table of Contents

# Underwriting

We are offering the shares of common stock described in this prospectus through J.P. Morgan Securities LLC, who is acting as sole book running manager. We have entered into an underwriting agreement with the underwriter. Subject to the terms and conditions of the underwriting agreement, we have agreed to sell to the underwriter, and the underwriter has agreed to purchase, at the public offering price less the underwriting discounts and commissions set forth on the cover page of this prospectus all 7,000,000 shares offered hereby.

Certain of our directors and executive officers, including our chief executive officer, our president and chief operating officer and our chief business officer, have indicated an interest in purchasing shares of our common stock in this offering. However, because these indications of interest are not binding agreements or commitments to purchase, these directors and officers may elect not to purchase any shares in this offering.

The underwriter is committed to purchase all the shares of common stock offered by us if it purchases any shares.

The underwriter proposes to offer the common shares directly to the public at the public offering price set forth on the cover page of this prospectus and to certain dealers at that price less a concession not in excess of $ per share. After the public offering of the shares, the offering price and other selling terms may be changed by the underwriter.

The underwriter has an option to buy up to 1,050,000 additional shares of common stock from us solely to cover sales of shares by the underwriter which exceed the number of shares specified. The underwriter has 30 days from the date of this prospectus supplement to exercise this option. If any additional shares of common stock are purchased, the underwriter will offer the additional shares on the same terms as those on which the shares are being offered.

The underwriting fee is equal to the public offering price per share of common stock less the amount paid by the underwriter to us per share of common stock. The underwriting fee is $ per share. The following table shows the per share and total underwriting discounts and commissions to be paid to the underwriter assuming both no exercise and full exercise of the underwriter s option to purchase additional shares.

| | **Without exercise of option to purchase additional shares** | **With full exercise of option to purchase additional shares** |
|---|---|---|
| Per Share | $ | $ |
| Total | | |

We estimate that the total expenses of this offering, including listing fees, printing fees and legal and accounting expenses, but excluding the underwriting discounts and commissions, will be approximately $ .

A prospectus in electronic format may be made available on the web site maintained by the underwriter.

We have agreed that we will not (i) offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase or otherwise transfer or dispose of, directly or indirectly, or file with the SEC a

Table of Contents

registration statement under the Securities Act relating to, any shares of our common stock or securities convertible into or exercisable or exchangeable for our common stock, or publicly disclose the intention to make any offer, sale, pledge, disposition or filing; (ii) enter into any swap or other arrangement that transfers, in whole or in part, any of the economic consequences associated with the ownership of any shares of common stock or any such other securities (whether any such transaction described in clause (i) or (ii) above is to be settled by delivery of common stock or such other securities, in cash or otherwise); or (iii) file any registration statement (other than a registration statement on Form S-8 or a registration statement filed in connection with a demand for registration pursuant to an existing agreement) with the SEC relating to the offering by us of any shares of common stock or any securities convertible into or exercisable or exchangeable for common stock without the prior written consent of J.P. Morgan Securities LLC for a period of 60 days after the date of this prospectus supplement. Notwithstanding the foregoing, if (1) during the last 17 days of the 60-day restricted period, we issue an earnings release or material news or a material event relating to our company occurs; or (2) prior to the expiration of the 60-day restricted period, we announce that we will release earnings results during the 16-day period beginning on the last day of the 60-day period, the restrictions described above shall continue to apply until the expiration of the 18-day period beginning on the issuance of the earnings release or the occurrence of the material news or material event.

The restrictions described in the preceding paragraph do not apply, subject to certain conditions, to the following:

- the sale of shares of common stock pursuant to the underwriting agreement;
- the issuance by us of shares of common stock upon the exercise of an option or the conversion of a security outstanding as of the date of this prospectus supplement;
- the issuance or distribution by us of shares of common stock in accordance with the terms of our employee stock purchase plan and 401(k) plan in existence as of the date of this prospectus;
- the grant of options, restricted stock or other equity-based awards under equity incentive plans established and currently maintained by us;
- the issuance of shares of common stock pursuant to the Investor Rights Agreement dated September 6, 2005 between us and Novartis; or
- the issuance by us of common stock representing up to 10% of our outstanding shares of common stock in connection with any strategic alliance, license, collaboration, acquisition or loan agreement entered into during the lock-up period.

Our directors and executive officers have entered into lock-up agreements with the underwriter prior to the commencement of this offering pursuant to which each of these persons or entities, with limited exceptions described below, for a period of 60 days after the date of this prospectus, may not, without the prior written consent of J.P. Morgan Securities LLC, (1) offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, or otherwise transfer or dispose of, directly or indirectly, any shares of common stock or any securities convertible into or exercisable or exchangeable for common stock (including without limitation, common stock or such other securities which may be deemed to be beneficially owned by the undersigned in accordance with the rules and regulations of the SEC and securities which may be issued upon exercise of a stock

Table of Contents

option or warrant), or publicly disclose the intention to make any offer, sale, pledge or disposition, (2) enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of the common stock or such other securities, whether any such transaction described in clause (1) or (2) above is to be settled by delivery of common stock or such other securities, in cash or otherwise or (3) make any demand for or exercise any right with respect to the registration of any shares of common stock or any security convertible into or exercisable or exchangeable for common stock. Notwithstanding the foregoing, if (1) during the last 17 days of the 60-day restricted period, we issue an earnings release or material news or a material event relating to us occurs; or (2) prior to the expiration of the 60-day restricted period, we announce that we will release earnings results during the 16-day period beginning on the last day of the 60-day period, the restrictions described above shall continue to apply until the expiration of the 18-day period beginning on the issuance of the earnings release or the occurrence of the material news or material event.

The restrictions described in the immediately preceding paragraph do not apply, subject to certain conditions, to the following:

- the sale of shares of common stock pursuant to the underwriting agreement;
- transfers of shares of common stock or such other securities as a bona fide gift or gifts;
- the exercise of any option to purchase shares of common stock, provided that the underlying common stock continues to be subject to the restrictions set forth above;
- transactions relating to shares of common stock or other securities acquired in open market transactions after the completion of this offering; provided that no filing by any party under the Exchange Act or other public announcement reporting a reduction in the beneficial ownership of common stock held by the signatory undersigned shall be required or shall be made voluntarily in connection with such transfer or disposition (other than a filing on Form 5 made after the expiration of the 60-day period referred to above);
- transfers of shares of common stock or any security convertible into or exercisable or exchangeable for common stock to the immediate family of the signatory, to a trust the beneficiaries of which are exclusively the signatory and/or a member or members of the immediate family of the signatory, or to any corporation, partnership, limited liability company or other entity all of the beneficial ownership interests of which are held exclusively by the signatory and/or a member or members of the immediate family of the signatory;
- transfers of shares of common stock or any security convertible into or exercisable or exchangeable for common stock upon death by will or intestate succession; or
- the entry into any trading plan established pursuant to Rule 10b5-1 of the Exchange Act, provided that no sales or other dispositions may occur under such plan until the expiration of the 60-day restricted period and that no filing or other public announcement, whether under the Exchange Act or otherwise, shall be required or shall be made by the signatory or us in connection with the trading plan during such restricted period.

We have agreed to indemnify the underwriter against certain liabilities, including liabilities under the Securities Act.

In connection with this offering, the underwriter may engage in stabilizing transactions, which involves making bids for, purchasing and selling shares of common stock in the open market for the purpose of preventing or retarding a decline in the market price of the common stock while

Table of Contents

this offering is in progress. These stabilizing transactions may include making short sales of the common stock, which involves the sale by the underwriter of a greater number of shares of common stock than they are required to purchase in this offering, and purchasing shares of common stock on the open market to cover positions created by short sales. Short sales may be covered shorts, which are short positions in an amount not greater than the underwriter s option to purchase additional shares referred to above, or may be naked shorts, which are short positions in excess of that amount. The underwriter may close out any covered short position either by exercising its option, in whole or in part, or by purchasing shares in the open market. In making this determination, the underwriter will consider, among other things, the price of shares available for purchase in the open market compared to the price at which the underwriter may purchase shares through the purchase option. A naked short position is more likely to be created if the underwriter is concerned that there may be downward pressure on the price of the common stock in the open market that could adversely affect investors who purchase in this offering. To the extent that the underwriter creates a naked short position, it will purchase shares in the open market to cover the position.

The underwriter has advised us that, pursuant to Regulation M of the Securities Act, they may also engage in other activities that stabilize, maintain or otherwise affect the price of the common stock, including the imposition of penalty bids.

These activities may have the effect of raising or maintaining the market price of the common stock or preventing or retarding a decline in the market price of the common stock, and, as a result, the price of the common stock may be higher than the price that otherwise might exist in the open market. If the underwriter commences these activities, they may discontinue them at any time. The underwriter may carry out these transactions on the NASDAQ Global Market, in the over-the-counter market or otherwise.

In addition, in connection with this offering the underwriter may engage in passive market making transactions in our common stock on the NASDAQ Global Market prior to the pricing and completion of this offering. Passive market making consists of displaying bids on the NASDAQ Global Market no higher than the bid prices of independent market makers and making purchases at prices no higher than these independent bids and effected in response to order flow. Net purchases by a passive market maker on each day are generally limited to a specified percentage of the passive market maker s average daily trading volume in the common stock during a specified period and must be discontinued when such limit is reached. Passive market making may cause the price of our common stock to be higher than the price that otherwise would exist in the open market in the absence of these transactions. If passive market making is commenced, it may be discontinued at any time.

Other than in the United States, no action has been taken by us or any underwriter that would permit a public offering of the securities offered by this prospectus in any jurisdiction where action for that purpose is required. The securities offered by this prospectus may not be offered or sold, directly or indirectly, nor may this prospectus or any other offering material or advertisements in connection with the offer and sale of any such securities be distributed or published in any jurisdiction, except under circumstances that will result in compliance with the applicable rules and regulations of that jurisdiction. Persons into whose possession this prospectus comes are advised to inform themselves about and to observe any restrictions relating to the offering and the distribution of this prospectus. This prospectus does not constitute an offer to sell or a solicitation of an offer to buy any securities offered by this prospectus in any jurisdiction in which such an offer or a solicitation is unlawful.

Table of Contents

In relation to each Member State of the European Economic Area which has implemented the Prospectus Directive (each, a Relevant Member State ) an offer to the public of any shares which are the subject of the offering contemplated by this prospectus supplement may not be made in that Relevant Member State, except that an offer to the public in that Relevant Member State of any Shares may be made at any time under the following exemptions under the Prospectus Directive, if they have been implemented in that Relevant Member State:

(a) to any legal entity which is a qualified investor as defined in the Prospectus Directive;

(b) to fewer than 100 or, if the Relevant Member State has implemented the relevant provision of the 2010 PD Amending Directive, 150, natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the representative for any such offer; or

(c) in any other circumstances falling within Article 3(2) of the Prospectus Directive, provided that no such offer of Shares shall result in a requirement for the publication by us or the representative of a prospectus pursuant to Article 3 of the Prospectus Directive.

For the purposes of this provision, the expression an offer to the public in relation to any shares in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and any shares to be offered so as to enable an investor to decide to purchase any shares, as the same may be varied in that Member State by any measure implementing the Prospectus Directive in that Member State, the expression Prospectus Directive means Directive 2003/71/EC (and amendments thereto, including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member State), and includes any relevant implementing measure in the Relevant Member State, and the expression 2010 PD Amending Directive means Directive 2010/73/EU.

## United Kingdom

The representative has represented and agreed that:

(a) it has only communicated or caused to be communicated and will only communicate or cause to be communicated an invitation or inducement to engage in investment activity (within the meaning of Section 21 of the Financial Services and Markets Act, or FSMA) received by it in connection with the issue or sale of the shares in circumstances in which Section 21(1) of the FSMA does not apply to us; and

(b) it has complied and will comply with all applicable provisions of the FSMA with respect to anything done by it in relation to the shares in, from or otherwise involving the United Kingdom.

The underwriter and its affiliates have provided in the past to us and our affiliates and may provide from time to time in the future certain commercial banking, financial advisory, investment banking and other services for us and such affiliates in the ordinary course of their business, for which they have received and may continue to receive customary fees and commissions. In addition, from time to time, the underwriter and its affiliates may effect transactions for their own account or the account of customers, and hold on behalf of themselves or their customers, long or short positions in our debt or equity securities or loans, and may do so in the future.

Table of Contents

## Legal matters

The validity of the shares of common stock offered hereby will be passed upon for us by Wilmer Cutler Pickering Hale and Dorr LLP. The underwriter is being represented in connection with this offering by Davis Polk & Wardwell LLP.

## Experts

The audited consolidated financial statements of Alnylam Pharmaceuticals, Inc., except as they relate to Regulus Therapeutics Inc., incorporated in this prospectus by reference to the Company s Annual Report on Form 10-K for the year ended December 31, 2011 and the effectiveness of internal control over financial reporting as of December 31, 2011 have been audited by PricewaterhouseCoopers LLP, an independent registered public accounting firm. Such consolidated financial statements, except as they relate to Regulus Therapeutics Inc., and management s assessment of the effectiveness of internal control over financial reporting (which is included in Management s Annual Report on Internal Control over Financial Reporting) have been so incorporated in reliance on the report of such independent registered public accounting firm given on the authority of said firm as experts in auditing and accounting.

The audited financial statements of Regulus Therapeutics Inc. for the year ended December 31, 2011 have been audited by Ernst & Young LLP, an independent registered public accounting firm, as stated in their report, which is incorporated herein by reference from the Alnylam Pharmaceuticals, Inc. Form 10-K for the year ended December 31, 2011. The audited consolidated financial statements of Alnylam Pharmaceuticals, Inc., to the extent they relate to Regulus Therapeutics Inc., have been so incorporated in reliance on the report of such independent registered public accounting firm given on the authority of said firm as experts in accounting and auditing.

## Where you can find more information

We file reports, proxy statements and other information with the SEC as required by the Exchange Act. You can find, copy and inspect information we file at the SEC s public reference room at 100 F Street, N.E., Room 1580, Washington, D.C. 20549. You can call the SEC at 1-800-SEC-0330 for further information about the public reference room. You can review our electronically filed reports, proxy and information statements on the SEC s website at *www.sec.gov* or on our website at *www.alnylam.com*. Information included on our website is not a part of this prospectus supplement or the accompanying prospectus.

This prospectus supplement is part of a registration statement that we filed with the SEC. The registration statement contains more information than this prospectus supplement and the accompanying prospectus regarding us and the securities, including certain exhibits and schedules. You can obtain a copy of the registration statement from the SEC at the address listed above or from the SEC s internet site.

## Incorporation of certain information by reference

The SEC allows us to incorporate into this prospectus supplement information that we file with the SEC in other documents. This means that we can disclose important information to you by referring to other documents that contain that information. The information incorporated by reference is considered to be part of this prospectus supplement and the accompanying prospectus. Information that we file with the SEC in the future and incorporate by reference in this prospectus

Table of Contents

supplement and the accompanying prospectus automatically updates and supersedes previously filed information as applicable. The following documents filed with the SEC pursuant to the Exchange Act are incorporated herein by reference (other than, in each case, documents or information deemed to have been furnished and not filed in accordance with SEC rules):

- our Annual Report on Form 10-K for the year ended December 31, 2011, filed with the SEC on February 13, 2012; and
- the description of our common stock contained in our Registration Statement on Form 8-A filed with the SEC on May 5, 2004, as amended by Amendment No. 1 to Form 8-A on Form 8-A/A filed with the SEC on June 3, 2004 and Amendment No. 2 to Form 8-A on Form 8-A/A filed with the SEC on July 14, 2005.

In addition, this prospectus supplement incorporates by reference all documents and reports that we file pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus supplement and prior to the completion or termination of this offering of common stock even though they are not specifically identified in this prospectus supplement, except in each case for information contained in any such filing where we indicate that such information is being furnished and is not to be considered filed under the Exchange Act.

You may request, orally or in writing, a copy of the documents which are incorporated by reference, which will be provided to you at no cost by contacting: Alnylam Pharmaceuticals, Inc., 300 Third Street, Cambridge, Massachusetts 02142, Attention: Investor Relations Department, (617) 551-8200.

Table of Contents

**PROSPECTUS**

# $150,000,000

## Debt Securities

## Common Stock

## Preferred Stock

## Purchase Contracts

## Purchase Units

## Warrants

We may issue securities from time to time in one or more offerings. This prospectus describes the general terms of these securities and the general manner in which these securities will be offered. We will provide the specific terms of these securities in supplements to this prospectus. The prospectus supplements will also describe the specific manner in which these securities will be offered and may also supplement, update or amend information contained in this document. You should read this prospectus and any applicable prospectus supplement before you invest.

We may offer these securities in amounts, at prices and on terms determined at the time of offering. The securities may be sold directly to you, through agents, or through underwriters and dealers. If agents, underwriters or dealers are used to sell the securities, we will name them and describe their compensation in a prospectus supplement.

Our common stock trades on the NASDAQ Global Market under the symbol ALNY.

**Investing in these securities involves certain risks. See Risk Factors included in any accompanying prospectus supplement and in the documents incorporated by reference in this prospectus for a discussion of the factors you should carefully consider before deciding to purchase these securities.**

**Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.**

The date of this prospectus is August 19, 2011

Table of Contents

**TABLE OF CONTENTS**

Table of Contents

## ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, which we refer to as the SEC, utilizing a shelf registration process. Under this shelf registration process, we may from time to time sell any combination of the securities described in this prospectus in one or more offerings for an aggregate initial offering price of up to $150,000,000.

This prospectus provides you with a general description of the securities we may offer. Each time we sell securities, we will provide one or more prospectus supplements that will contain specific information about the terms of the offering. The prospectus supplement may also add, update or change information contained in this prospectus. You should read both this prospectus and the accompanying prospectus supplement together with the additional information described under the heading Where You Can Find More Information appearing below.

You should rely only on the information contained in or incorporated by reference in this prospectus, any accompanying prospectus supplement or in any related free writing prospectus filed by us with the SEC. We have not authorized anyone to provide you with different information. This prospectus and the accompanying prospectus supplement do not constitute an offer to sell or the solicitation of an offer to buy any securities other than the securities described in the accompanying prospectus supplement or an offer to sell or the solicitation of an offer to buy such securities in any circumstances in which such offer or solicitation is unlawful. You should assume that the information appearing in this prospectus, any prospectus supplement, the documents incorporated by reference and any related free writing prospectus is accurate only as of their respective dates. Our business, financial condition, results of operations and prospects may have changed materially since those dates.

Unless the context otherwise indicates, references in this prospectus to Alnylam, we, our, us and the Company refer, collectively, to Alnylam Pharmaceuticals, Inc., a Delaware corporation, and its consolidated subsidiaries.

## WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC s website at *http://www.sec.gov*. Copies of certain information filed by us with the SEC are also available on our website at *http://www.alnylam.com*. The information on our website is not incorporated by reference into this prospectus and should not be considered to be a part of this prospectus. Our website address is included in this prospectus as an inactive technical reference only. You may also read and copy any document we file at the SEC s Public Reference Room, 100 F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information on the operation of the Public Reference Room.

This prospectus is part of a registration statement we filed with the SEC. This prospectus omits some information contained in the registration statement in accordance with SEC rules and regulations. You should review the information and exhibits in the registration statement for further information on us and our consolidated subsidiaries and the securities we are offering. Statements in this prospectus concerning any document we filed as an exhibit to the registration statement or that we otherwise filed with the SEC are not intended to be comprehensive and are qualified by reference to these filings. You should review the complete document to evaluate these statements.

## INCORPORATION BY REFERENCE

The SEC allows us to incorporate by reference much of the information we file with the SEC, which means that we can disclose important information to you by referring you to those publicly available documents. The information that we incorporate by reference in this prospectus is considered to be part of this prospectus. Because we are incorporating by reference future filings with the SEC, this prospectus is continually updated and those future filings may modify or supersede some of the information included or incorporated in this prospectus.

Table of Contents

This means that you must look at all of the SEC filings that we incorporate by reference to determine if any of the statements in this prospectus or in any document previously incorporated by reference have been modified or superseded. This prospectus incorporates by reference the documents listed below (File No. 000-50743) and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act (in each case, other than those documents or the portions of those documents not deemed to be filed) between the date of the initial registration statement and the effectiveness of the registration statement and following the effectiveness of the registration statement until the offering of the securities under the registration statement is terminated or completed:

- Annual Report on Form 10-K for the fiscal year ended December 31, 2010, including the information specifically incorporated by reference into the Annual Report on Form 10-K from our definitive proxy statement for the 2011 Annual Meeting of Stockholders;
- Quarterly Report on Form 10-Q for the fiscal quarter ended March 31, 2011;
- Current Reports on Form 8-K filed on February 7, 2011, March 3, 2011, March 15, 2011, March 17, 2011, March 23, 2011, March 25, 2011, April 7, 2011, May 2, 2011, June 7, 2011, June 10, 2011, June 13, 2011 and June 29, 2011; and
- The description of our common stock and rights plan contained in Amendment No. 2 to our Registration Statement to Form 8-A on Form 8-A/A filed on July 14, 2005, including any amendments or reports filed for the purpose of updating such description.

You may request a copy of these filings, at no cost, by writing or telephoning us at the following address and phone number:

**Alnylam Pharmaceuticals, Inc.**

**300 Third Street**

**Cambridge, Massachusetts 02142**

**Attn: Investor Relations**

**(617) 551-8200**

## FORWARD-LOOKING STATEMENTS

This prospectus and the information incorporated by reference in this prospectus include forward looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Exchange Act. Without limiting the foregoing, the words may, will, should, could, expects, plans, intends, anticipates, believes, estimates, predicts, potential, and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these words. All forward-looking statements included in this prospectus are based on information available to us up to, and including, the date of this document, and we assume no obligation to update any such forward-looking statements to reflect events or circumstances that arise after the date hereof. Our actual results could differ materially from those anticipated in these forward-looking statements as a result of certain important factors, including those contained in or incorporated by reference into this prospectus. You should carefully review those factors and also carefully review the risks outlined in other documents that we file from time to time with the SEC.

## ABOUT ALNYLAM PHARMACEUTICALS, INC.

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.

2

Table of Contents

Our core product strategy is focused on the development and commercialization of innovative RNAi therapeutics for the treatment of genetically defined targets and diseases. As part of this strategy, our goal is to develop product candidates with the following shared characteristics: a genetically defined target and disease; the potential to have a significant impact in high unmet need patient populations; the ability to leverage our existing RNAi delivery platform; the opportunity to monitor an early biomarker in Phase I clinical trials for human proof of concept; and the existence of clinically relevant endpoints for the filing of a new drug application, with a focused patient database and possible accelerated paths for commercialization. We intend to commercialize products arising from this core product strategy on our own in the United States and potentially certain other countries, and we intend to enter into alliances to develop and commercialize any such products in other global territories.

We are currently advancing three core programs in clinical or pre-clinical development: ALN-TTR for the treatment of transthyretin-mediated amyloidosis; ALN-PCS for the treatment of severe hypercholesterolemia; and ALN-HPN for the treatment of refractory anemia. While focusing our efforts on our core product strategy, we also intend to continue to advance additional development programs through existing or future alliances. We have three partner-based programs in clinical or pre-clinical development, including ALN-RSV01 for the treatment of respiratory syncytial virus infection, ALN-VSP for the treatment of liver cancers and ALN-HTT for the treatment of Huntington s disease.

Our principal executive offices are located at 300 Third Street Cambridge, Massachusetts 02142, and our telephone number is (617) 551-8200.

## CONSOLIDATED RATIOS OF EARNINGS TO FIXED CHARGES

The following table sets forth our ratio of earnings to fixed charges for each of the periods indicated. You should read this table in conjunction with the consolidated financial statements and notes incorporated by reference in this prospectus.

| | Three Months Ended March 31, 2011 | Fiscal Year Ended December 31, 2010 | December 31, 2009 | December 31, 2008 | December 31, 2007 | December 31, 2006 |
|---|---|---|---|---|---|---|
| Consolidated ratios of earnings to fixed charges | N/A | N/A | N/A | N/A | N/A | N/A |

For purposes of calculating the ratios above, earnings consist of pre-tax loss from continuing operations before adjustment for loss from equity investee plus fixed charges. Fixed charges include interest expense on indebtedness and an estimate of interest expense within rental expense.

We did not record earnings for the three months ended March 31, 2011 or for any of the years ended December 31, 2010, 2009, 2008, 2007 and 2006. Accordingly, our earnings were insufficient to cover fixed charges in such periods and we are unable to disclose a ratio of earnings to fixed charges for such periods. Due to our losses for the three months ended March 31, 2011 and the years ended December 31, 2010, 2009, 2008, 2007 and 2006, the ratio coverage was less than 1:1. We would have needed to generate additional earnings of $15,213,000, $35,362,000, $42,098,000, $16,240,000, $79,146,000 and $34,608,000, respectively, to achieve a coverage ratio of 1:1 in those periods.

Our ratios of earnings to combined fixed charges and preferred stock dividends for the periods indicated above are the same as our ratios of earnings to fixed charges set forth above because we had no shares of preferred stock outstanding during the periods indicated and currently have no shares of preferred stock outstanding.

## USE OF PROCEEDS

We intend to use the net proceeds from the sale of any securities offered under this prospectus for general corporate purposes, ultimately focused on advancing our clinical pipeline, unless otherwise indicated in the

Table of Contents

applicable prospectus supplement. General corporate purposes may include working capital and capital expenditures, research and development expenses, including clinical trial costs, general and administrative expenses, the potential acquisition of, or investment in, companies, technologies, products or assets that complement our business. We may temporarily invest the net proceeds in investment-grade, interest-bearing securities until they are used for their stated purpose. We have not determined the amount of net proceeds to be used specifically for such purposes. As a result, management will retain broad discretion over the allocation of net proceeds.

## DILUTION

If there is a material dilution of the purchasers equity interest from the sale of common equity securities offered under this prospectus, we will set forth in any prospectus supplement the following information regarding any such material dilution of the equity interests of purchasers purchasing securities in an offering under this prospectus:

- the net tangible book value per share of our equity securities before and after the offering;
- the amount of the increase in such net tangible book value per share attributable to the cash payments made by the purchasers in the offering; and
- the amount of the immediate dilution from the public offering price which will be absorbed by such purchasers.

## DESCRIPTION OF CAPITAL STOCK

The following description of our capital stock is intended as a summary only. This description is based upon, and is qualified by reference to, our certificate of incorporation, our bylaws and applicable provisions of Delaware corporate law. This summary is not complete. You should read our certificate of incorporation and bylaws, which are filed as exhibits to the registration statement of which this prospectus forms a part, for the provisions that are important to you.

Our authorized capital stock consists of 125,000,000 shares of common stock and 5,000,000 shares of preferred stock. As of June 30, 2011, 42,653,915 shares of common stock were outstanding and no shares of preferred stock were outstanding.

### Common Stock

*Annual Meeting.* Annual meetings of our stockholders are held on the date designated in accordance with our bylaws. Written notice must be mailed to each stockholder entitled to vote not less than ten nor more than 60 days before the date of the meeting. The presence in person or by proxy of the holders of record of a majority of our issued and outstanding shares entitled to vote at such meeting constitutes a quorum for the transaction of business at meetings of the stockholders. Special meetings of the stockholders may be called for any purpose by the board of directors and shall be called by the chairman of the board or the secretary upon the written request, stating the purpose of such meeting, of the holders of a majority of the outstanding shares of all classes of capital stock entitled to vote at the meeting. Except as may be otherwise provided by applicable law, our certificate of incorporation or our bylaws, all elections shall be decided by a plurality, and all other questions shall be decided by a majority, of the votes cast by stockholders entitled to vote thereon at a duly held meeting of stockholders at which a quorum is present.

*Voting Rights.* Each holder of the common stock is entitled to one vote for each share held on all matters to be voted upon by stockholders.

*Dividends.* The holders of the common stock, after any preferences of holders of any preferred stock, are entitled to receive dividends when, as and if declared by the board of directors out of legally available funds.

Table of Contents

*Liquidation and Dissolution.* If we are liquidated or dissolved, the holders of the common stock will be entitled to share in our assets available for distribution to stockholders in proportion to the amount of common stock they own. The amount available for common stockholders is calculated after payment of liabilities. Holders of any preferred stock will receive a preferential share of our assets before the holders of the common stock receive any assets.

*Other Rights.* Holders of the common stock have no right to:

convert the stock into any other security;

have the stock redeemed; or

except as provided below, purchase additional stock or to maintain their proportionate ownership interest.

The common stock does not have cumulative voting rights. Holders of shares of the common stock are not required to make additional capital contributions.

Beginning in September 2005, we entered into the first of two strategic alliances with Novartis Pharma AG and its affiliate, Novartis Institutes for Biomedical Research, Inc., whom we refer to together as Novartis. At that time, we and Novartis executed a stock purchase agreement and an investor rights agreement, and ultimately executed a research collaboration and license agreement. The investor rights agreement provides Novartis with the right to acquire additional equity securities of Alnylam 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 generally to maintain its ownership percentage in Alnylam until the earlier of any sale by Novartis of shares of our common stock and the expiration or termination of the collaboration and license agreement, subject to certain exceptions. As of June 30, 2011, Novartis owned approximately 13.1% of our common stock.

*Transfer Agent and Registrar.* Computershare Trust Company, N.A. is the transfer agent and registrar for the common stock.

**Preferred Stock**

As of June 30, 2011, no shares of preferred stock were outstanding. Other terms of any series of preferred stock will be described in the prospectus supplement relating to that series of preferred stock. The terms of any series of preferred stock may differ from the terms described below. Certain provisions of the preferred stock described below and in any applicable prospectus supplement are not complete.

We are authorized to issue blank check preferred stock, which may be issued in one or more series upon authorization of our board of directors. Our board of directors is authorized to fix the designation of the series, the number of authorized shares of the series, dividend rights and terms, conversion rights, voting rights, redemption rights and terms, liquidation preferences and any other rights, powers, preferences and limitations applicable to each series of preferred stock. The authorized shares of our preferred stock are available for issuance without further action by our stockholders, unless such action is required by applicable law or the rules of any stock exchange on which our securities may be listed. If the approval of our stockholders is not required for the issuance of shares of our preferred stock, our board may determine not to seek stockholder approval.

Our board of directors has authorized the issuance of Series A junior participating preferred stock, see Series A Junior Participating Preferred Stock, which includes terms and conditions that could discourage a takeover or other transaction that holders of some or a majority of our common stock might believe to be in their best interests. Any other series of our preferred stock could also, depending on the terms of such series, impede the completion of a merger, tender offer or other takeover attempt. Our board of directors will make any determination to issue such shares based upon its judgment as to the best interests of our stockholders. Our directors, in so acting, could issue preferred stock having terms that could discourage an acquisition attempt through which an acquirer may be able to change the composition of our board of directors, including a tender offer or other transaction that some, or a majority, of our stockholders might believe to be in their best interests or in which stockholders might receive a premium for their stock over the then-current market price of the stock.

5

Table of Contents

The preferred stock has the terms described below unless otherwise provided in the prospectus supplement relating to a particular series of preferred stock. You should read the prospectus supplement relating to the particular series of preferred stock being offered for specific terms, including:

- the designation and stated value per share of the preferred stock and the number of shares offered;
- the amount of liquidation preference per share;
- the price at which the preferred stock will be issued;
- the dividend rate, or method of calculation of dividends, the dates on which dividends will be payable, whether dividends will be cumulative or noncumulative and, if cumulative, the dates from which dividends will commence to accumulate;
- any redemption or sinking fund provisions;
- if other than the currency of the United States, the currency or currencies including composite currencies in which the preferred stock is denominated and/or in which payments will or may be payable;
- any conversion provisions; and
- any other rights, preferences, privileges, limitations and restrictions on the preferred stock.

The preferred stock will, when issued, be fully paid and nonassessable. Unless otherwise specified in the prospectus supplement, each series of preferred stock will rank equally as to dividends and liquidation rights in all respects with each other series of preferred stock. The rights of holders of shares of each series of preferred stock will be subordinate to those of our general creditors.

*Rank.* Unless otherwise specified in the prospectus supplement, the preferred stock will, with respect to dividend rights and rights upon our liquidation, dissolution or winding up of its affairs, rank:

- senior to our common stock and to all equity securities ranking junior to such preferred stock with respect to dividend rights or rights upon our liquidation, dissolution or winding up of our affairs;
- on a parity with all equity securities issued by us, the terms of which specifically provide that such equity securities rank on a parity with the preferred stock with respect to dividend rights or rights upon our liquidation, dissolution or winding up of our affairs; and
- junior to all equity securities issued by us, the terms of which specifically provide that such equity securities rank senior to the preferred stock with respect to dividend rights or rights upon our liquidation, dissolution or winding up of our affairs.

The term equity securities does not include convertible debt securities.

*Dividends.* Holders of the preferred stock of each series will be entitled to receive, when, as and if declared by our board of directors, cash dividends at such rates and on such dates described in the applicable prospectus supplement. Different series of preferred stock may be entitled

to dividends at different rates or based on different methods of calculation. The dividend rate may be fixed or variable or both. Dividends will be payable to the holders of record as they appear on our stock books on record dates fixed by our board of directors, as specified in the applicable prospectus supplement.

Dividends on any series of preferred stock may be cumulative or noncumulative, as described in the applicable prospectus supplement. If our board of directors does not declare a dividend payable on a dividend payment date on any series of noncumulative preferred stock, then the holders of that noncumulative preferred stock will have no right to receive a dividend for that dividend payment date, and we will have no obligation to pay the dividend accrued for that period, whether or not dividends on that series are declared payable on any future dividend payment dates. Dividends on any series of cumulative preferred stock will accrue from the date we initially issue shares of such series or such other date specified in the applicable prospectus supplement.

No dividends may be declared or paid or funds set apart for the payment of any dividends on any parity securities unless full dividends have been paid or set apart for payment on the preferred stock. If full dividends are not paid, the preferred stock will share dividends pro rata with the parity securities.

No dividends may be declared or paid or funds set apart for the payment of dividends on any junior securities unless full dividends for all dividend periods terminating on or prior to the date of the declaration or

Table of Contents

payment will have been paid or declared and a sum sufficient for the payment set apart for payment on the preferred stock.

*Liquidation Preference.* Upon any voluntary or involuntary liquidation, dissolution or winding up of our affairs, then, before we make any distribution or payment to the holders of any common stock or any other class or series of our capital stock ranking junior to the preferred stock in the distribution of assets upon any liquidation, dissolution or winding up of our affairs, the holders of each series of preferred stock shall be entitled to receive out of assets legally available for distribution to stockholders, liquidating distributions in the amount of the liquidation preference per share set forth in the prospectus supplement, plus any accrued and unpaid dividends thereon. Such dividends will not include any accumulation in respect of unpaid noncumulative dividends for prior dividend periods. Unless otherwise specified in the prospectus supplement, after payment of the full amount of their liquidating distributions, the holders of preferred stock will have no right or claim to any of our remaining assets. Upon any such voluntary or involuntary liquidation, dissolution or winding up, if our available assets are insufficient to pay the amount of the liquidating distributions on all outstanding preferred stock and the corresponding amounts payable on all other classes or series of our capital stock ranking on parity with the preferred stock and all other such classes or series of shares of capital stock ranking on parity with the preferred stock in the distribution of assets, then the holders of the preferred stock and all other such classes or series of capital stock will share ratably in any such distribution of assets in proportion to the full liquidating distributions to which they would otherwise be entitled.

Upon any such liquidation, dissolution or winding up and if we have made liquidating distributions in full to all holders of preferred stock, we will distribute our remaining assets among the holders of any other classes or series of capital stock ranking junior to the preferred stock according to their respective rights and preferences and, in each case, according to their respective number of shares. For such purposes, our consolidation or merger with or into any other corporation, trust or entity, or the sale, lease or conveyance of all or substantially all of our property or assets, will not be deemed to constitute a liquidation, dissolution or winding up of our affairs.

*Redemption.* If so provided in the applicable prospectus supplement, the preferred stock will be subject to mandatory redemption or redemption at our option, as a whole or in part, in each case upon the terms, at the times and at the redemption prices set forth in such prospectus supplement.

The prospectus supplement relating to a series of preferred stock that is subject to mandatory redemption will specify the number of shares of preferred stock that shall be redeemed by us in each year commencing after a date to be specified, at a redemption price per share to be specified, together with an amount equal to all accrued and unpaid dividends thereon to the date of redemption. Unless the shares have a cumulative dividend, such accrued dividends will not include any accumulation in respect of unpaid dividends for prior dividend periods. We may pay the redemption price in cash or other property, as specified in the applicable prospectus supplement. If the redemption price for preferred stock of any series is payable only from the net proceeds of the issuance of shares of our capital stock, the terms of such preferred stock may provide that, if no such shares of our capital stock shall have been issued or to the extent the net proceeds from any issuance are insufficient to pay in full the aggregate redemption price then due, such preferred stock shall automatically and mandatorily be converted into the applicable shares of our capital stock pursuant to conversion provisions specified in the applicable prospectus supplement. Notwithstanding the foregoing, we will not redeem any preferred stock of a series unless:

- if that series of preferred stock has a cumulative dividend, we have declared and paid or contemporaneously declare and pay or set aside funds to pay full cumulative dividends on the preferred stock for all past dividend periods and the then current dividend period; or

- if such series of preferred stock does not have a cumulative dividend, we have declared and paid or contemporaneously declare and pay or set aside funds to pay full dividends for the then current dividend period.

In addition, we will not acquire any preferred stock of a series unless:

- if that series of preferred stock has a cumulative dividend, we have declared and paid or contemporaneously declare and pay or set aside funds to pay full cumulative dividends on all outstanding

Table of Contents

shares of such series of preferred stock for all past dividend periods and the then current dividend period; or

if that series of preferred stock does not have a cumulative dividend, we have declared and paid or contemporaneously declare and pay or set aside funds to pay full dividends on the preferred stock of such series for the then current dividend period.

However, at any time we may purchase or acquire preferred stock of that series (1) pursuant to a purchase or exchange offer made on the same terms to holders of all outstanding preferred stock of such series or (2) by conversion into or exchange for shares of our capital stock ranking junior to the preferred stock of such series as to dividends and upon liquidation.

If fewer than all of the outstanding shares of preferred stock of any series are to be redeemed, we will determine the number of shares that may be redeemed pro rata from the holders of record of such shares in proportion to the number of such shares held or for which redemption is requested by such holder or by any other equitable manner that we determine. Such determination will reflect adjustments to avoid redemption of fractional shares.

Unless otherwise specified in the prospectus supplement, we will mail notice of redemption at least 30 days but not more than 60 days before the redemption date to each holder of record of preferred stock to be redeemed at the address shown on our stock transfer books. Each notice shall state:

the redemption date;

the number of shares and series of preferred stock to be redeemed;

the redemption price;

the place or places where certificates for such preferred stock are to be surrendered for payment of the redemption price;

that dividends on the shares to be redeemed will cease to accrue on such redemption date;

the date on which the holder s conversion rights, if any, as to such shares shall terminate; and

the specific number of shares to be redeemed from each such holder if fewer than all the shares of any series are to be redeemed.

If notice of redemption has been given and we have set aside the funds necessary for such redemption in trust for the benefit of the holders of any shares called for redemption, then from and after the redemption date, dividends will cease to accrue on such shares, and all rights of the holders of such shares will terminate, except the right to receive the redemption price.

*Voting Rights.* Holders of preferred stock will not have any voting rights, except as required by law or as indicated in the applicable prospectus supplement.

Unless otherwise provided for under the terms of any series of preferred stock, no consent or vote of the holders of shares of preferred stock or any series thereof shall be required for any amendment to our certificate of incorporation that would increase the number of authorized shares of preferred stock or the number of authorized shares of any series thereof or decrease the number of authorized shares of preferred stock or the number of authorized shares of any series thereof (but not below the number of authorized shares of preferred stock or such series, as the case may be, then outstanding).

*Conversion Rights.* The terms and conditions, if any, upon which any series of preferred stock is convertible into our common stock will be set forth in the applicable prospectus supplement relating thereto. Such terms will include the number of shares of common stock into which the shares of preferred stock are convertible, the conversion price, rate or manner of calculation thereof, the conversion period, provisions as to

Table of Contents

whether conversion will be at our option or at the option of the holders of the preferred stock, the events requiring an adjustment of the conversion price and provisions affecting conversion in the event of the redemption.

*Transfer Agent and Registrar.* The transfer agent and registrar for the preferred stock will be set forth in the applicable prospectus supplement.

**Series A Junior Participating Preferred Stock**

In July 2005, our board of directors 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 for each outstanding share of our 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. 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 will have no rights as a stockholder of Alnylam, including the right to vote or to receive dividends. Subject to the terms and conditions of 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, referred to as an Acquiring Person, acquires, or obtained the right to acquire, beneficial ownership of 20% or more of the outstanding shares of our common stock or (b) the first date on which an executive officer of Alnylam 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% of the outstanding shares of our common stock. 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, subject to certain exceptions, each Right not owned by the Acquiring Person will entitle its holder to receive, upon exercise, that number of shares of our common stock (or in certain circumstances, cash, property or other securities) 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.

**Effects of Authorized but Unissued Stock**

We have shares of common stock and preferred stock available for future issuance without stockholder approval, subject to any limitations imposed by the listing standards of The NASDAQ Global Market. We may utilize these additional shares for a variety of corporate purposes, including for future public offerings to raise additional capital or facilitate corporate acquisitions or for payment as a dividend on our capital stock. The existence of unissued and unreserved common stock and preferred stock may enable our board of directors to issue shares to persons friendly to current management or to issue preferred stock with terms that could have the effect of making it more difficult for a third party to acquire, or could discourage a third party from seeking to acquire, a controlling interest in our company by means of a merger, tender offer, proxy contest or otherwise. In addition, if we issue preferred stock, the issuance could adversely affect the voting power of holders of common stock and the likelihood that such holders will receive dividend payments and payments upon liquidation.

**Provisions of Our Certificate of Incorporation and Bylaws and Delaware Law That May Have Anti-Takeover Effects**

*Board of Directors.* Our certificate of incorporation and bylaws provide for a board of directors divided as nearly equally as possible into three classes. Each class is elected to a term expiring at the annual meeting of stockholders held in the third year following the year of such election. The number of directors comprising our board of directors is fixed from time to time by the board of directors.

*Removal of Directors by Stockholders.* Delaware law provides that members of our board of directors may only be removed for cause by a vote of the holders of a majority of the outstanding shares entitled to vote on the election of the directors.

Table of Contents

*Stockholder Nomination of Directors.* Our bylaws provide that a stockholder must notify us in writing of any stockholder nomination of a director not earlier than the 120th day and not later the 90th day prior to the first anniversary of the preceding year s annual meeting; provided, that if the date of the annual meeting is advanced by more than 20 days, or delayed by more than 60 days from the first anniversary of the preceding year s annual meeting, notice must be received not earlier than the 120th day prior to such annual meeting and not later than the close of business on the later of (1) the 90th day prior to such annual meeting and (2) the 10th day following the date on which notice of the date of such annual meeting was mailed or public disclosure of the date of such annual meeting was made, whichever occurs first. Our bylaws also specify requirements relating to the content of the notice which stockholders must provide, including a stockholder nomination for election to our board of directors, to be properly presented at the annual meeting.

*No Action By Written Consent.* Our certificate of incorporation provides that our stockholders may not act by written consent and may only act at duly called meetings of stockholders.

*Delaware Business Combination Statute.* Section 203 of the General Corporation Law of the State of Delaware, which we refer to as the DGCL, is applicable to us. Section 203 of the DGCL restricts some types of transactions and business combinations between a corporation and a 15% stockholder. A 15% stockholder is generally considered by Section 203 to be a person owning 15% or more of the corporation s outstanding voting stock. Section 203 refers to a 15% stockholder as an interested stockholder. Section 203 restricts these transactions for a period of three years from the date the stockholder acquires 15% or more of our outstanding voting stock. With some exceptions, unless the transaction is approved by the board of directors and the holders of at least two-thirds of our outstanding voting stock, Section 203 prohibits significant business transactions such as:

- a merger with, disposition of significant assets to or receipt of disproportionate financial benefits by the interested stockholder, and
- any other transaction that would increase the interested stockholder s proportionate ownership of any class or series of our capital stock.

The shares held by the interested stockholder are not counted as outstanding when calculating the two-thirds of the outstanding voting stock needed for approval.

The prohibition against these transactions does not apply if:

- prior to the time that any stockholder became an interested stockholder, the board of directors approved either the business combination or the transaction in which such stockholder acquired 15% or more of our outstanding voting stock, or
- the interested stockholder owns at least 85% of our outstanding voting stock as a result of a transaction in which such stockholder acquired 15% or more of our outstanding voting stock. Shares held by persons who are both directors and officers or by some types of employee stock plans are not counted as outstanding when making this calculation.

**Directors Liability**

Our certificate of incorporation provides that a member of the board of directors will not be personally liable to us or our stockholders for monetary damages for breaches of their legal duties to us or our stockholders as a director, except for liability:

- for any breach of the director s legal duty to act in the best interests of us and our stockholders;
- for acts or omissions by the director with dishonest intentions or which involve intentional misconduct or an intentional violation of the law;

for declaring dividends or authorizing the purchase or redemption of shares in violation of Delaware law; or

for transactions where the director derived an improper personal benefit.

Table of Contents

Our certificate of incorporation provides that we must indemnify our directors to the fullest extent permitted by Delaware law, and we are required to advance expenses, as incurred, to our directors in connection with a legal proceeding to the fullest extent permitted by Delaware law.

## DESCRIPTION OF DEBT SECURITIES

Our debt securities, consisting of notes, debentures or other evidences of indebtedness, may be issued from time to time in one or more series pursuant to, in the case of senior debt securities, a senior indenture to be entered into between us and a trustee to be named therein, and in the case of subordinated debt securities, a subordinated indenture to be entered into between us and a trustee to be named therein. The terms of our debt securities will include those set forth in the indentures and those made a part of the indentures by the Trust Indenture Act of 1939, as amended.

Because the following is only a summary of selected provisions of the indentures and the debt securities, it does not contain all information that may be important to you. This summary is not complete and is qualified in its entirety by reference to the base indentures and any supplemental indentures thereto or officer s certificate or resolution of our board of directors related thereto. We urge you to read the indentures because the indentures, not this description, define the rights of the holders of the debt securities. The senior indenture and the subordinated indenture will be substantially in the forms included as exhibits to the registration statement of which this prospectus is a part.

### General

The senior debt securities will constitute unsecured and unsubordinated obligations of ours and will rank *pari passu* with our other unsecured and unsubordinated obligations. The subordinated debt securities will constitute our unsecured and subordinated obligations and will be junior in right of payment to our Senior Indebtedness (including senior debt securities), as described under the heading Certain Terms of the Subordinated Debt Securities Subordination.

The debt securities will be our unsecured obligations. Any secured debt or other secured obligations will be effectively senior to the debt securities to the extent of the value of the assets securing such debt or other obligations.

The applicable prospectus supplement will include any additional or different terms of the debt securities being offered, including the following terms:

- the debt securities designation;
- the aggregate principal amount of the debt securities;
- the percentage of their principal amount (i.e., price) at which the debt securities will be issued;
- the date or dates on which the debt securities will mature and the right, if any, to extend such date or dates;
- the rate or rates, if any, per year, at which the debt securities will bear interest, or the method of determining such rate or rates;
- the date or dates from which such interest will accrue, the interest payment dates on which such interest will be payable or the manner of determination of such interest payment dates and the record dates for the determination of holders to whom interest is payable on any interest payment date;
- the right, if any, to extend the interest payment periods and the duration of that extension;

the manner of paying principal and interest and the place or places where principal and interest will be payable;

provisions for a sinking fund purchase or other analogous fund, if any;

Table of Contents

- the period or periods, if any, within which, the price or prices at which, and the terms and conditions upon which the debt securities may be redeemed, in whole or in part, at our option or at your option;
- the form of the debt securities;
- any provisions for payment of additional amounts for taxes and any provision for redemption, if we must pay such additional amounts in respect of any debt security;
- the terms and conditions, if any, upon which we may have to repay the debt securities early at your option;
- the currency, currencies or currency units for which you may purchase the debt securities and the currency, currencies or currency units in which principal and interest, if any, on the debt securities may be payable;
- the terms and conditions upon which conversion or exchange of the debt securities may be effected, if any, including the initial conversion or exchange price or rate and any adjustments thereto and the period or periods when a conversion or exchange may be effected;
- whether and upon what terms the debt securities may be defeased;
- any events of default or covenants in addition to or in lieu of those set forth in the indenture;
- provisions for electronic issuance of debt securities or for debt securities in uncertificated form; and
- any other terms of the debt securities, including any terms which may be required by or advisable under applicable laws or regulations or advisable in connection with the marketing of the debt securities.

We may from time to time, without notice to or the consent of the holders of any series of debt securities, create and issue further debt securities of any such series ranking equally with the debt securities of such series in all respects (or in all respects other than the payment of interest accruing prior to the issue date of such further debt securities or except for the first payment of interest following the issue date of such further debt securities). Such further debt securities may be consolidated and form a single series with the debt securities of such series and have the same terms as to status, redemption or otherwise as the debt securities of such series.

You may present debt securities for exchange and you may present debt securities for transfer in the manner, at the places and subject to the restrictions set forth in the debt securities and the applicable prospectus supplement. We will provide you those services without charge, although you may have to pay any tax or other governmental charge payable in connection with any exchange or transfer, as set forth in the indenture.

Debt securities will bear interest at a fixed rate or a floating rate. Debt securities bearing no interest or interest at a rate that at the time of issuance is below the prevailing market rate (original issue discount securities) may be sold at a discount below their stated principal amount. Special U.S. federal income tax considerations applicable to any such discounted debt securities or to certain debt securities issued at par which are treated as having been issued at a discount for U.S. federal income tax purposes will be described in the applicable prospectus supplement.

We may issue debt securities with the principal amount payable on any principal payment date, or the amount of interest payable on any interest payment date, to be determined by reference to one or more currency exchange rates, securities or baskets of securities, commodity prices or indices. You may receive a payment of principal on any principal payment date, or a payment of interest on any interest payment date, that is greater than or less than the amount of principal or interest otherwise payable on such dates, depending on the value on such dates of the

applicable currency, security or basket of securities, commodity or index. Information as to the methods for determining the amount of principal or interest payable on any date, the currencies, securities or baskets of securities, commodities or indices to which the amount payable on such date is linked and certain additional tax considerations will be set forth in the applicable prospectus supplement.

Table of Contents

**Certain Terms of the Senior Debt Securities**

*Covenants.* Unless otherwise indicated in a prospectus supplement, the senior debt securities will not contain any financial or restrictive covenants, including covenants restricting either us or any of our subsidiaries from incurring, issuing, assuming or guarantying any indebtedness secured by a lien on any of our or our subsidiaries property or capital stock, or restricting either us or any of our subsidiaries from entering into sale and leaseback transactions.

*Consolidation, Merger and Sale of Assets.* Unless we indicate otherwise in a prospectus supplement, we may not consolidate with or merge into any other person, in a transaction in which we are not the surviving corporation, or convey, transfer or lease our properties and assets substantially as an entirety to any person, unless:

- the successor entity, if any, is a U.S. corporation, limited liability company, partnership or trust (subject to certain exceptions provided for in the senior indenture);
- the successor entity assumes our obligations on the senior debt securities and under the senior indenture;
- immediately after giving effect to the transaction, no default or event of default shall have occurred and be continuing; and
- certain other conditions are met.

*No Protection in the Event of a Change of Control.* Unless otherwise indicated in a prospectus supplement with respect to a particular series of senior debt securities, the senior debt securities will not contain any provisions which may afford holders of the senior debt securities protection in the event we have a change in control or in the event of a highly leveraged transaction (whether or not such transaction results in a change in control).

*Events of Default.* Unless otherwise indicated in a prospectus supplement with respect to a particular series of senior debt securities, an event of default for any series of senior debt securities is defined under the senior indenture as being:

- our default in the payment of principal or premium on the senior debt securities of such series when due and payable whether at maturity, upon acceleration, redemption or otherwise, if that default continues for a period of five days (or such other period as may be specified for such series);
- our default in the payment of interest on any senior debt securities of such series when due and payable, if that default continues for a period of 60 days (or such other period as may be specified for such series);
- our default in the performance of or breach of any of our other covenants or agreements in the senior indenture applicable to senior debt securities of such series, other than a covenant breach which is specifically dealt with elsewhere in the senior indenture, and that default or breach continues for a period of 90 days after we receive written notice from the trustee or from the holders of 25% or more in aggregate principal amount of the senior debt securities of all series affected thereby;
- there occurs any other event of default provided for in such series of senior debt securities;

a court having jurisdiction enters a decree or order for (1) relief in respect of us in an involuntary case under any applicable bankruptcy, insolvency or other similar law now or hereafter in effect; (2) appointment of a receiver, liquidator, assignee, custodian, trustee, sequestrator or similar official of us or for all or substantially all of our property and assets; or (3) the winding up or liquidation of our affairs and such decree or order shall remain unstayed and in effect for a period of 60 consecutive days; or

we (1) commence a voluntary case under any applicable bankruptcy, insolvency or other similar law now or hereafter in effect, or consent to the entry of an order for relief in an involuntary case under any such law; (2) consent to the appointment of or taking possession by a receiver, liquidator, assignee, custodian, trustee, sequestrator or similar official of ours for all or substantially all of our property and assets; or (3) effect any general assignment for the benefit of creditors.

Table of Contents

The default by us under any other debt, including any other series of debt securities, is not a default under the senior indenture.

If an event of default other than an event of default specified in the last two bullet points above occurs with respect to a series of senior debt securities and is continuing under the senior indenture, then, and in each and every such case, either the trustee or the holders of not less than 25% in aggregate principal amount of such series then outstanding under the senior indenture (each such series voting as a separate class) by written notice to us and to the trustee, if such notice is given by the holders, may, and the trustee at the request of such holders shall, declare the principal amount of and accrued interest, if any, on such senior debt securities to be immediately due and payable.

If an event of default specified in the last two bullet points above occurs with respect to us and is continuing, the entire principal amount of, and accrued interest, if any, on each series of senior debt securities then outstanding shall become immediately due and payable.

Upon a declaration of acceleration, the principal amount of and accrued interest, if any, on such senior debt securities shall be immediately due and payable. Unless otherwise specified in the prospectus supplement relating to a series of senior debt securities originally issued at a discount, the amount due upon acceleration shall include only the original issue price of the senior debt securities, the amount of original issue discount accrued to the date of acceleration and accrued interest, if any.

Upon certain conditions, declarations of acceleration may be rescinded and annulled and past defaults may be waived by the holders of a majority in aggregate principal amount of all the senior debt securities of such series affected by the default, each series voting as a separate class (or, of all the senior debt securities, as the case may be, voting as a single class). Furthermore, subject to various provisions in the senior indenture, the holders of at least a majority in aggregate principal amount of a series of senior debt securities, by notice to the trustee, may waive an existing default or event of default with respect to such senior debt securities and its consequences, except a default in the payment of principal of or interest on such senior debt securities or in respect of a covenant or provision of the senior indenture which cannot be modified or amended without the consent of the holders of each such senior debt security. Upon any such waiver, such default shall cease to exist, and any event of default with respect to such senior debt securities shall be deemed to have been cured, for every purpose of the senior indenture; but no such waiver shall extend to any subsequent or other default or event of default or impair any right consequent thereto. For information as to the waiver of defaults, see Modification and Waiver.

The holders of at least a majority in aggregate principal amount of a series of senior debt securities may direct the time, method and place of conducting any proceeding for any remedy available to the trustee or exercising any trust or power conferred on the trustee with respect to such senior debt securities. However, the trustee may refuse to follow any direction that conflicts with law or the senior indenture, that may involve the trustee in personal liability, or that the trustee determines in good faith may be unduly prejudicial to the rights of holders of such series of senior debt securities not joining in the giving of such direction and may take any other action it deems proper that is not inconsistent with any such direction received from holders of such series of senior debt securities. A holder may not pursue any remedy with respect to the senior indenture or any series of senior debt securities unless:

- the holder gives the trustee written notice of a continuing event of default;
- the holders of at least 25% in aggregate principal amount of such series of senior debt securities make a written request to the trustee to pursue the remedy in respect of such event of default;
- the requesting holder or holders offer the trustee indemnity satisfactory to the trustee against any costs, liability or expense;
- the trustee does not comply with the request within 60 days after receipt of the request and the offer of indemnity; and
- during such 60-day period, the holders of a majority in aggregate principal amount of such series of senior debt securities do not give the trustee a direction that is inconsistent with the request.

**Table of Contents**

These limitations, however, do not apply to the right of any holder of a senior debt security to receive payment of the principal of or interest, if any, on such senior debt security, or to bring suit for the enforcement of any such payment, on or after the due date for the senior debt securities, which right shall not be impaired or affected without the consent of the holder.

The senior indenture requires certain of our officers to certify, on or before a fixed date in each year in which any senior debt security is outstanding, as to their knowledge of our compliance with all conditions and covenants under the senior indenture.

*Discharge and Defeasance.* The senior indenture provides that, unless the terms of any series of senior debt securities provides otherwise, we may discharge our obligations with respect to a series of senior debt securities and the senior indenture with respect to such series of senior debt securities if:

- we pay or cause to be paid, as and when due and payable, the principal of and any interest on all senior debt securities of such series outstanding under the senior indenture;

- all senior debt securities of such series previously authenticated and delivered with certain exceptions, have been delivered to the trustee for cancellation and we have paid all sums payable by us under the senior indenture; or

- the senior debt securities of such series mature within one year or all of them are to be called for redemption within one year under arrangements satisfactory to the trustee for giving the notice of redemption, and we irrevocably deposit in trust with the trustee, as trust funds solely for the benefit of the holders of the senior debt securities of such series, for that purpose, the entire amount in cash or, in the case of any series of senior debt securities payments on which may only be made in U.S. dollars, U.S. government obligations (maturing as to principal and interest in such amounts and at such times as will insure the availability of sufficient cash), after payment of all federal, state and local taxes or other charges and assessments in respect thereof payable by the trustee, to pay principal of and interest on the senior debt securities of such series to maturity or redemption, as the case may be, and to pay all other sums payable by us under the senior indenture.

With respect to the first and second bullet points, only our obligations to compensate and indemnify the trustee and our right to recover unclaimed money held by the trustee under the senior indenture shall survive. With respect to the third bullet point, certain rights and obligations under the senior indenture (such as our obligation to maintain an office or agency in respect of such senior debt securities, to have moneys held for payment in trust, to register the transfer or exchange of such senior debt securities, to deliver such senior debt securities for replacement or to be canceled, to compensate and indemnify the trustee and to appoint a successor trustee, and our right to recover unclaimed money held by the trustee) shall survive until such senior debt securities are no longer outstanding. Thereafter, only our obligations to compensate and indemnify the trustee and our right to recover unclaimed money held by the trustee shall survive.

Unless the terms of any series of senior debt securities provide otherwise, on the 121st day after the date of deposit of the trust funds with the trustee, we will be deemed to have paid and will be discharged from any and all obligations in respect of the series of senior debt securities provided for in the funds, and the provisions of the senior indenture will no longer be in effect with respect to such senior debt securities ( legal defeasance ); provided that the following conditions shall have been satisfied:

- we have irrevocably deposited in trust with the trustee as trust funds solely for the benefit of the holders of the senior debt securities of such series, for payment of the principal of and interest on the senior debt securities of such series, cash in an amount or, in the case of any series of senior debt securities payments on which can only be made in U.S. dollars, U.S. government obligations (maturing as to principal and interest at such times and in such amounts as will insure the availability of cash) or a combination thereof sufficient (in the opinion of a nationally recognized firm of independent public accountants expressed in a written certification thereof delivered to the trustee), after payment of all federal, state and local taxes or other charges and assessments in respect thereof payable by the trustee, to pay and discharge the principal of and accrued interest on the senior debt securities of such series to maturity or earlier redemption, as the case may be, and any mandatory sinking fund payments on the day on which such payments are due and payable in accordance with the terms of the senior indenture and the senior debt securities of such series;

15

Table of Contents

such deposit will not result in a breach or violation of, or constitute a default under, the senior indenture or any other material agreement or instrument to which we are a party or by which we are bound;

no default or event of default with respect to the senior debt securities of such series shall have occurred and be continuing on the date of such deposit;

we shall have delivered to the trustee either an officer s certificate and an opinion of counsel that the holders of the senior debt securities of such series will not recognize income, gain or loss for federal income tax purposes as a result of our exercising our option under this provision of the senior indenture and will be subject to federal income tax on the same amount and in the same manner and at the same times as would have been the case if such deposit and defeasance had not occurred or a ruling by the Internal Revenue Service to the same effect; and

we have delivered to the trustee an officer s certificate and an opinion of counsel, in each case stating that all conditions precedent provided for in the senior indenture relating to the contemplated defeasance of the senior debt securities of such series have been complied with.

Subsequent to the legal defeasance above, certain rights and obligations under the senior indenture (such as our obligation to maintain an office or agency in respect of such senior debt securities, to have moneys held for payment in trust, to register the exchange of such senior debt securities, to deliver such senior debt securities for replacement or to be canceled, to compensate and indemnify the trustee and to appoint a successor trustee, and our right to recover unclaimed money held by the trustee) shall survive until such senior debt securities are no longer outstanding. After such senior debt securities are no longer outstanding, only our obligations to compensate and indemnify the trustee and our right to recover unclaimed money held by the trustee shall survive.

*Modification and Waiver.* We and the trustee may amend or supplement the senior indenture or the senior debt securities without the consent of any holder:

to convey, mortgage or pledge any assets as security for the senior debt securities of one or more series;

to evidence the succession of another corporation to us, and the assumption by such successor corporation of our covenants, agreements and obligations under the senior indenture;

to cure any ambiguity, defect or inconsistency in the senior indenture or in any supplemental indenture or to conform the senior indenture or the senior debt securities to the description of senior debt securities of such series set forth in this prospectus or a prospectus supplement;

to evidence and provide for the acceptance of appointment hereunder by a successor trustee, or to make such changes as shall be necessary to provide for or facilitate the administration of the trusts in the senior indenture by more than one trustee;

to provide for or add guarantors with respect to the senior debt securities of any series;

to establish the form or forms or terms of the senior debt securities as permitted by the senior indenture;

to add to, delete from or revise the conditions, limitations and restrictions on the authorized amount, terms, purposes of issue, authentication and delivery of any series of senior debt securities;

to add to our covenants such new covenants, restrictions, conditions or provisions for the protection of the holders, and to make the occurrence, or the occurrence and continuance, of a default in any such additional covenants, restrictions, conditions or provisions an event of default;

to make any change to the senior debt securities of any series so long as no senior debt securities of such series are outstanding; or

to make any change that does not adversely affect the rights of any holder in any material respect.

**Table of Contents**

Other amendments and modifications of the senior indenture or the senior debt securities issued may be made, and our compliance with any provision of the senior indenture with respect to any series of senior debt securities may be waived, with the consent of the holders of not less than a majority of the aggregate principal amount of the outstanding senior debt securities of all series affected by the amendment or modification (voting as one class); provided, however, that each affected holder must consent to any modification, amendment or waiver that:

extends the stated maturity of the principal of, or any installment of interest on, any senior debt securities of such series;

reduces the principal amount of, or premium, if any, or interest on, any senior debt securities of such series;

changes the currency of payment of principal of, or premium, if any, or interest on, any senior debt securities of such series;

changes the provisions for calculating the optional redemption price, including the definitions relating thereto;

changes the provisions relating to the waiver of past defaults or changes or impairs the right of holders to receive payment or to institute suit for the enforcement of any payment of any senior debt securities of such series on or after the due date therefor;

reduces the above-stated percentage of outstanding senior debt securities of such series the consent of whose holders is necessary to modify or amend or to waive certain provisions of or defaults under the senior indenture;

waives a default in the payment of principal of or interest on the senior debt securities;

adversely affects the rights of such holder under any mandatory redemption or repurchase provision or any right of redemption or repurchase at the option of such holder; or

modifies any of the provisions of this paragraph, except to increase any required percentage or to provide that certain other provisions cannot be modified or waived without the consent of the holder of each senior debt security of such series affected by the modification.

It shall not be necessary for the consent of the holders under this section of the senior indenture to approve the particular form of any proposed amendment, supplement or waiver, but it shall be sufficient if such consent approves the substance thereof. After an amendment, supplement or waiver under this section of the senior indenture becomes effective, the trustee must give to the holders affected thereby certain notice briefly describing the amendment, supplement or waiver. We will mail supplemental indentures to holders upon request. Any failure by the trustee to give such notice, or any defect therein, shall not, however, in any way impair or affect the validity of any such supplemental indenture or waiver.

*No Personal Liability of Incorporators, Stockholders, Officers, Directors.* The senior indenture provides that no recourse shall be had under or upon any obligation, covenant or agreement of ours in the senior indenture or any supplemental indenture, or in any of the senior debt securities or because of the creation of any indebtedness represented thereby, against any incorporator, stockholder, officer or director, past, present or future, of ours or of any predecessor or successor corporation thereof under any law, statute or constitutional provision or by the enforcement of any assessment or by any legal or equitable proceeding or otherwise. Each holder, by accepting the senior debt securities, waives and releases all such liability.

Table of Contents

*Concerning the Trustee.* The senior indenture provides that, except during the continuance of a default, the trustee will not be liable, except for the performance of such duties as are specifically set forth in the senior indenture. If an event of default has occurred and is continuing, the trustee will exercise such rights and powers vested in it under the senior indenture and will use the same degree of care and skill in its exercise as a prudent person would exercise under the circumstances in the conduct of such person s own affairs.

We may have normal banking relationships with the trustee under the senior indenture in the ordinary course of business.

*Unclaimed Funds.* All funds deposited with the trustee or any paying agent for the payment of principal, interest, premium or additional amounts in respect of the senior debt securities that remain unclaimed for two years after the maturity date of such senior debt securities will be repaid to us. Thereafter, any right of any noteholder to such funds shall be enforceable only against us, and the trustee and paying agents will have no liability therefor.

*Governing Law.* The senior indenture and the debt securities will be governed by, and construed in accordance with, the internal laws of the State of New York.

**Certain Terms of the Subordinated Debt Securities**

Other than the terms of the subordinated indenture and subordinated debt securities relating to subordination, or otherwise as described in the prospectus supplement relating to a particular series of subordinated debt securities, the terms of the subordinated indenture and subordinated debt securities are identical in all material respects to the terms of the senior indenture and senior debt securities. Additional or different subordination terms may be specified in the prospectus supplement applicable to a particular series.

*Subordination.* The indebtedness evidenced by the subordinated debt securities is subordinate to the prior payment in full of all our Senior Indebtedness, as defined in the subordinated indenture. During the continuance beyond any applicable grace period of any default in the payment of principal, premium, interest or any other payment due on any of our Senior Indebtedness, we may not make any payment of principal of, or premium, if any, or interest on the subordinated debt securities. In addition, upon any payment or distribution of our assets upon any dissolution, winding up, liquidation or reorganization, the payment of the principal of, or premium, if any, and interest on the subordinated debt securities will be subordinated to the extent provided in the subordinated indenture in right of payment to the prior payment in full of all our Senior Indebtedness. Because of this subordination, if we dissolve or otherwise liquidate, holders of our subordinated debt securities may receive less, ratably, than holders of our Senior Indebtedness. The subordination provisions do not prevent the occurrence of an event of default under the subordinated indenture.

The term Senior Indebtedness of a person means with respect to such person the principal of, premium, if any, interest on, and any other payment due pursuant to any of the following, whether outstanding on the date of the subordinated indenture or incurred by that person in the future:

all of the indebtedness of that person for money borrowed;

all of the indebtedness of that person evidenced by notes, debentures, bonds or other securities sold by that person for money;

all of the lease obligations which are capitalized on the books of that person in accordance with generally accepted accounting principles;

Table of Contents

all indebtedness of others of the kinds described in the first two bullet points above and all lease obligations of others of the kind described in the third bullet point above that the person, in any manner, assumes or guarantees or that the person in effect guarantees through an agreement to purchase, whether that agreement is contingent or otherwise; and

all renewals, extensions or refundings of indebtedness of the kinds described in the first, second or fourth bullet point above and all renewals or extensions of leases of the kinds described in the third or fourth bullet point above;

unless, in the case of any particular indebtedness, lease, renewal, extension or refunding, the instrument or lease creating or evidencing it or the assumption or guarantee relating to it expressly provides that such indebtedness, lease, renewal, extension or refunding is not superior in right of payment to the subordinated debt securities. Our senior debt securities constitute Senior Indebtedness for purposes of the subordinated debt indenture.

## DESCRIPTION OF PURCHASE CONTRACTS AND PURCHASE UNITS

We may issue purchase contracts, including contracts obligating holders to purchase from or sell to us, and obligating us to sell to or purchase from the holders, a specified number of shares of our common stock or preferred stock at a future date or dates, which we refer to in this prospectus as purchase contracts. The price per share of common stock or preferred stock and the number of shares of each may be fixed at the time the purchase contracts are issued or may be determined by reference to a specific formula set forth in the purchase contracts. The purchase contracts may be issued separately or as part of units, often known as purchase units, consisting of one or more purchase contracts and beneficial interests in debt securities or any other securities described in the applicable prospectus supplement or any combination of the foregoing, securing the holders obligations to purchase the common stock or preferred stock under the purchase contracts.

The purchase contracts may require us to make periodic payments to the holders of the purchase units or vice versa, and these payments may be unsecured or prefunded on some basis. The purchase contracts may require holders to secure their obligations under those contracts in a specified manner, including pledging their interest in another purchase contract.

The applicable prospectus supplement will describe the terms of the purchase contracts and purchase units, including, if applicable, collateral or depositary arrangements.

## DESCRIPTION OF WARRANTS

We may issue warrants to purchase debt securities, preferred stock or common stock. We may offer warrants separately or together with one or more additional warrants, debt securities, preferred stock or common stock, or any combination of those securities in the form of units, as described in the applicable prospectus supplement. If we issue warrants as part of a unit, the accompanying prospectus supplement will specify whether those warrants may be separated from the other securities in the unit prior to the expiration date of the warrants. The applicable prospectus supplement will also describe the following terms of any warrants:

the specific designation and aggregate number of, and the offering price at which we will issue, the warrants;

the currency or currency units in which the offering price, if any, and the exercise price are payable;

the date on which the right to exercise the warrants will begin and the date on which that right will expire or, if you may not continuously exercise the warrants throughout that period, the specific date or dates on which you may exercise the warrants;

Table of Contents

whether the warrants are to be sold separately or with other securities as parts of units;

whether the warrants will be issued in definitive or global form or in any combination of these forms, although, in any case, the form of a warrant included in a unit will correspond to the form of the unit and of any security included in that unit;

any applicable material U.S. federal income tax consequences;

the identity of the warrant agent for the warrants and of any other depositaries, execution or paying agents, transfer agents, registrars or other agents;

the proposed listing, if any, of the warrants or any securities purchasable upon exercise of the warrants on any securities exchange;

the designation and terms of any equity securities purchasable upon exercise of the warrants;

the designation, aggregate principal amount, currency and terms of any debt securities that may be purchased upon exercise of the warrants;

if applicable, the designation and terms of the debt securities, preferred stock or common stock with which the warrants are issued and, the number of warrants issued with each security;

if applicable, the date from and after which any warrants issued as part of a unit and the related debt securities, preferred stock or common stock will be separately transferable;

the number of shares of preferred stock or the number of shares of common stock purchasable upon exercise of a warrant and the price at which those shares may be purchased;

if applicable, the minimum or maximum amount of the warrants that may be exercised at any one time;

information with respect to book-entry procedures, if any;

the antidilution provisions of, and other provisions for changes to or adjustment in the exercise price of, the warrants, if any;

any redemption or call provisions; and

any additional terms of the warrants, including terms, procedures and limitations relating to the exchange or exercise of the warrants.

## FORMS OF SECURITIES

Each debt security, purchase contract, purchase unit and warrant will be represented either by a certificate issued in definitive form to a particular investor or by one or more global securities representing the entire issuance of securities. Unless the applicable prospectus supplement provides otherwise, certificated securities in definitive form and global securities will be issued in registered form. Definitive securities name you or your nominee as the owner of the security, and in order to transfer or exchange these securities or to receive payments other than interest or other interim payments, you or your nominee must physically deliver the securities to the trustee, registrar, paying agent or other agent, as applicable. Global securities name a depositary or its nominee as the owner of the debt securities, purchase contracts, purchase units or warrants represented by these global securities. The depositary maintains a computerized system that will reflect each investor s beneficial ownership of the securities through an account maintained by the investor with its broker/dealer, bank, trust company or other representative, as we explain more fully below.

**Registered Global Securities**

We may issue the registered debt securities, purchase contracts, purchase units and warrants in the form of one or more fully registered global securities that will be deposited with a depositary or its nominee identified in

Table of Contents

the applicable prospectus supplement and registered in the name of that depositary or nominee. In those cases, one or more registered global securities will be issued in a denomination or aggregate denominations equal to the portion of the aggregate principal or face amount of the securities to be represented by registered global securities. Unless and until it is exchanged in whole for securities in definitive registered form, a registered global security may not be transferred except as a whole by and among the depositary for the registered global security, the nominees of the depositary or any successors of the depositary or those nominees.

If not described below, any specific terms of the depositary arrangement with respect to any securities to be represented by a registered global security will be described in the prospectus supplement relating to those securities. We anticipate that the following provisions will apply to all depositary arrangements.

Ownership of beneficial interests in a registered global security will be limited to persons, called participants, that have accounts with the depositary or persons that may hold interests through participants. Upon the issuance of a registered global security, the depositary will credit, on its book-entry registration and transfer system, the participants accounts with the respective principal or face amounts of the securities beneficially owned by the participants. Any dealers, underwriters or agents participating in the distribution of the securities will designate the accounts to be credited. Ownership of beneficial interests in a registered global security will be shown on, and the transfer of ownership interests will be effected only through, records maintained by the depositary, with respect to interests of participants, and on the records of participants, with respect to interests of persons holding through participants. The laws of some states may require that some purchasers of securities take physical delivery of these securities in definitive form. These laws may impair your ability to own, transfer or pledge beneficial interests in registered global securities.

So long as the depositary, or its nominee, is the registered owner of a registered global security, that depositary or its nominee, as the case may be, will be considered the sole owner or holder of the securities represented by the registered global security for all purposes under the applicable indenture, purchase contract, warrant agreement or purchase unit agreement. Except as described below, owners of beneficial interests in a registered global security will not be entitled to have the securities represented by the registered global security registered in their names, will not receive or be entitled to receive physical delivery of the securities in definitive form and will not be considered the owners or holders of the securities under the applicable indenture, purchase contract, purchase unit agreement or warrant agreement. Accordingly, each person owning a beneficial interest in a registered global security must rely on the procedures of the depositary for that registered global security and, if that person is not a participant, on the procedures of the participant through which the person owns its interest, to exercise any rights of a holder under the applicable indenture, purchase contract, purchase unit agreement or warrant agreement. We understand that under existing industry practices, if we request any action of holders or if an owner of a beneficial interest in a registered global security desires to give or take any action that a holder is entitled to give or take under the applicable indenture, purchase contract, purchase unit agreement or warrant agreement, the depositary for the registered global security would authorize the participants holding the relevant beneficial interests to give or take that action, and the participants would authorize beneficial owners owning through them to give or take that action or would otherwise act upon the instructions of beneficial owners holding through them.

Principal, premium, if any, and interest payments on debt securities, and any payments to holders with respect to warrants, purchase agreements or purchase units, represented by a registered global security registered in the name of a depositary or its nominee will be made to the depositary or its nominee, as the case may be, as the registered owner of the registered global security. None of Alnylam, the trustees, the warrant agents, the unit agents or any other agent of ours, agent of the trustees or agent of the warrant agents or unit agents will have any responsibility or liability for any aspect of the records relating to payments made on account of beneficial ownership interests in the registered global security or for maintaining, supervising or reviewing any records relating to those beneficial ownership interests.

We expect that the depositary for any of the securities represented by a registered global security, upon receipt of any payment of principal, premium, interest or other distribution of underlying securities or other

Table of Contents

property to holders on that registered global security, will immediately credit participants accounts in amounts proportionate to their respective beneficial interests in that registered global security as shown on the records of the depositary. We also expect that payments by participants to owners of beneficial interests in a registered global security held through participants will be governed by standing customer instructions and customary practices, as is now the case with the securities held for the accounts of customers or registered in street name, and will be the responsibility of those participants.

If the depositary for any of the securities represented by a registered global security is at any time unwilling or unable to continue as depositary or ceases to be a clearing agency registered under the Exchange Act, and a successor depositary registered as a clearing agency under the Exchange Act is not appointed by us within 90 days, we will issue securities in definitive form in exchange for the registered global security that had been held by the depositary. Any securities issued in definitive form in exchange for a registered global security will be registered in the name or names that the depositary gives to the relevant trustee, warrant agent, unit agent or other relevant agent of ours or theirs. It is expected that the depositary s instructions will be based upon directions received by the depositary from participants with respect to ownership of beneficial interests in the registered global security that had been held by the depositary.

## PLAN OF DISTRIBUTION

We may sell securities:

- through underwriters;
- through dealers;
- through agents;
- directly to purchasers; or
- through a combination of any of these methods of sale.

In addition, we may issue the securities as a dividend or distribution or in a subscription rights offering to our existing security holders.

We may directly solicit offers to purchase securities, or agents may be designated to solicit such offers. We will, in the prospectus supplement relating to such offering, name any agent that could be viewed as an underwriter under the Securities Act, and describe any commissions that we must pay. Any such agent will be acting on a best efforts basis for the period of its appointment or, if indicated in the applicable prospectus supplement, on a firm commitment basis. This prospectus may be used in connection with any offering of our securities through any of these methods or other methods described in the applicable prospectus supplement.

The distribution of the securities may be effected from time to time in one or more transactions:

- at a fixed price, or prices, which may be changed from time to time;
- at market prices prevailing at the time of sale;
- at prices related to such prevailing market prices; or

at negotiated prices.

Each prospectus supplement will describe the method of distribution of the securities and any applicable restrictions.

Table of Contents

The prospectus supplement with respect to the securities of a particular series will describe the terms of the offering of the securities, including the following:

- the name of the agent or any underwriters;
- the public offering or purchase price;
- any discounts and commissions to be allowed or paid to the agent or underwriters;
- all other items constituting underwriting compensation;
- any discounts and commissions to be allowed or paid to dealers; and
- any exchanges on which the securities will be listed.

If any underwriters or agents are utilized in the sale of the securities in respect of which this prospectus is delivered, we will enter into an underwriting agreement or other agreement with them at the time of sale to them, and we will set forth in the prospectus supplement relating to such offering the names of the underwriters or agents and the terms of the related agreement with them.

If a dealer is utilized in the sale of the securities in respect of which the prospectus is delivered, we will sell such securities to the dealer, as principal. The dealer may then resell such securities to the public at varying prices to be determined by such dealer at the time of resale.

If we offer securities in a subscription rights offering to our existing security holders, we may enter into a standby underwriting agreement with dealers, acting as standby underwriters. We may pay the standby underwriters a commitment fee for the securities they commit to purchase on a standby basis. If we do not enter into a standby underwriting arrangement, we may retain a dealer-manager to manage a subscription rights offering for us.

Agents, underwriters, dealers and other persons may be entitled under agreements which they may enter into with us to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, and may be customers of, engage in transactions with or perform services for us in the ordinary course of business.

If so indicated in the applicable prospectus supplement, we will authorize underwriters or other persons acting as our agents to solicit offers by certain institutions to purchase securities from us pursuant to delayed delivery contracts providing for payment and delivery on the date stated in the prospectus supplement. Each contract will be for an amount not less than, and the aggregate amount of securities sold pursuant to such contracts shall not be less nor more than, the respective amounts stated in the prospectus supplement. Institutions with whom the contracts, when authorized, may be made include commercial and savings banks, insurance companies, pension funds, investment companies, educational and charitable institutions and other institutions, but shall in all cases be subject to our approval. Delayed delivery contracts will not be subject to any conditions except that:

- the purchase by an institution of the securities covered under that contract shall not at the time of delivery be prohibited under the laws of the jurisdiction to which that institution is subject; and
- if the securities are also being sold to underwriters acting as principals for their own account, the underwriters shall have purchased such securities not sold for delayed delivery. The underwriters and other persons acting as our agents will not have any responsibility in respect of the validity or performance of delayed delivery contracts.

Certain agents, underwriters and dealers, and their associates and affiliates may be customers of, have borrowing relationships with, engage in other transactions with, and/or perform services, including investment banking services, for us or one or more of our respective affiliates in the ordinary course of business.

In order to facilitate the offering of the securities, any underwriters may engage in transactions that stabilize, maintain or otherwise affect the price of the securities or any other securities the prices of which may be used to determine payments on such securities. Specifically, any underwriters may overallot in connection with the

Table of Contents

offering, creating a short position for their own accounts. In addition, to cover overallotments or to stabilize the price of the securities or of any such other securities, the underwriters may bid for, and purchase, the securities or any such other securities in the open market. Finally, in any offering of the securities through a syndicate of underwriters, the underwriting syndicate may reclaim selling concessions allowed to an underwriter or a dealer for distributing the securities in the offering if the syndicate repurchases previously distributed securities in transactions to cover syndicate short positions, in stabilization transactions or otherwise. Any of these activities may stabilize or maintain the market price of the securities above independent market levels. Any such underwriters are not required to engage in these activities and may end any of these activities at any time.

Under Rule 15c6-1 of the Exchange Act, trades in the secondary market generally are required to settle in three business days, unless the parties to any such trade expressly agree otherwise. The applicable prospectus supplement may provide that the original issue date for your securities may be more than three scheduled business days after the trade date for your securities. Accordingly, in such a case, if you wish to trade securities on any date prior to the third business day before the original issue date for your securities, you will be required, by virtue of the fact that your securities initially are expected to settle in more than three scheduled business days after the trade date for your securities, to make alternative settlement arrangements to prevent a failed settlement.

The securities may be new issues of securities and may have no established trading market. The securities may or may not be listed on a national securities exchange. We can make no assurance as to the liquidity of or the existence of trading markets for any of the securities.

In compliance with the guidelines of the Financial Industry Regulatory Authority, or FINRA, the aggregate maximum discount, commission or agency fees or other items constituting underwriting compensation to be received by any FINRA member or independent broker-dealer will not exceed 8% of the proceeds from any offering pursuant to this prospectus and any applicable prospectus supplement.

## LEGAL MATTERS

Unless the applicable prospectus supplement indicates otherwise, the validity of the securities in respect of which this prospectus is being delivered will be passed upon by Wilmer Cutler Pickering Hale and Dorr LLP.

## EXPERTS

The audited consolidated financial statements of Alnylam Pharmaceuticals, Inc., incorporated in this prospectus by reference to the Company s Annual Report on Form 10-K for the year ended December 31, 2010, except as they relate to Regulus Therapeutics Inc., and the effectiveness of internal control over financial reporting as of December 31, 2010 have been audited by PricewaterhouseCoopers LLP, an independent registered public accounting firm. Such consolidated financial statements, except as they relate to Regulus Therapeutics Inc., and management s assessment of the effectiveness of internal control over financial reporting (which is included in Management s Annual Report on Internal Control over Financial Reporting) have been so incorporated in reliance on the report of such independent registered public accounting firm given on the authority of said firm as experts in auditing and accounting.

The audited financial statements of Regulus Therapeutics Inc., incorporated in this prospectus by reference to the Company s Annual Report on Form 10-K for the year ended December 31, 2010, have been audited by Ernst & Young LLP, independent auditors, as stated in their report, which is incorporated herein by reference. The audited consolidated financial statements of Alnylam Pharmaceuticals, Inc., to the extent they relate to Regulus Therapeutics Inc., have been so incorporated in reliance on the report of such independent auditors given on the authority of said firm as experts in accounting and auditing.

Table of Contents

*7,000,000 shares*

*Common Stock*

# Prospectus Supplement

# J.P. Morgan

, 2012

**We have not authorized anyone to provide any information other than that contained or incorporated by reference in this prospectus supplement and accompanying prospectus or any free writing prospectus that we or the underwriters provide you in connection with the offering. We take no responsibility for, and cannot provide any assurance as to the reliability of, any other information that others may give you. We are not making an offer of these securities in any state where the offer is not permitted. You should not assume that the information contained in or incorporated by reference in this prospectus supplement and accompanying prospectus is accurate as of any date other than the date on the front of this prospectus supplement.**

**No action is being taken in any jurisdiction outside the United States to permit a public offering of shares of our common stock or possession or distribution of this prospectus supplement in that jurisdiction. Persons who come into possession of this prospectus supplement in jurisdictions outside the United States are required to inform themselves about and to observe any restrictions as to this offering and the distribution of this prospectus supplement applicable to that jurisdiction.**