ALNYLAM PHARMACEUTICALS, INC.
Form 424B5
February 01, 2006

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Filed pursuant to Rule 424(b)(5)
Registration Statement Nos. 333-129905 and 333-131233

*PROSPECTUS SUPPLEMENT*
*(To Prospectus dated December 20, 2005)*

*5,115,961 Shares*
*ALNYLAM PHARMACEUTICALS, INC.*
*Common Stock*

***We are offering 5,115,961 shares of our common stock.***

***Our common stock is quoted on the Nasdaq National Market under the trading symbol ALNY.***
***On January 31, 2006, the last reported sale price of our common stock on the Nasdaq National Market was $13.44 per share.***

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

*PRICE $13.00 A SHARE*

| | ***Price to Public*** | ***Underwriting Discounts and Commissions*** | ***Proceeds to Alnylam*** |
|---|---|---|---|
| *Per Share* | *$ 13.00* | *$ 0.78* | *$ 12.22* |
| *Total* | *$ 66,507,493* | *$ 3,990,450* | *$ 62,517,043* |

*We have granted the underwriters the right to purchase up to an additional 767,394 shares to cover over-allotments.*

*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 underwriters expect to deliver the shares to purchasers on February 6, 2006.*

*Co-lead and sole book runner*
*MORGAN STANLEY*

Co-lead
*BANC OF AMERICA SECURITIES LLC*

*PIPER JAFFRAY* *SG COWEN & CO.*

*RODMAN & RENSHAW*

January 31, 2006.

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You should rely only on the information contained in this prospectus supplement and the accompanying prospectus, and the documents incorporated by reference in this prospectus supplement or the accompanying prospectus, or to which we have referred you. We have not, and the underwriters have not, authorized anyone to provide you with different information. If anyone provides you with different or inconsistent information, you should not rely on it. 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. You should not assume that the information contained in this prospectus supplement or the accompanying prospectus, or any document incorporated by reference in this prospectus supplement or the accompanying prospectus, is accurate as of any date other than the date on the front cover of the applicable document. Neither the delivery of this prospectus supplement nor any distribution of securities pursuant to this prospectus supplement shall, under any circumstances, create any implication that there has been no change in the information set forth or incorporated by reference into this prospectus supplement or in our affairs since the date of this prospectus supplement. Our business, financial condition, results of operations and prospects may have changed since that date.

This document is in two parts. The first part is the prospectus supplement, which describes the specific terms of the common stock we are offering and also adds to and updates information contained in the accompanying prospectus. The second part, the 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, on the one hand, and the information contained in the accompanying prospectus, on the other hand, you should rely on the information in this prospectus supplement.

Unless otherwise stated, all references to us, our, Alnylam, we, the Company and similar designations refer t Alnylam Pharmaceuticals, Inc. and our subsidiaries. Our logo, trademarks and service marks are the property of Alnylam. Other trademarks or service marks appearing in this prospectus are the property of their respective holders.

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## PROSPECTUS SUPPLEMENT SUMMARY

*This summary highlights selected information about us and this offering. This information is not complete and does not contain all the information you should consider before investing in our common stock. You should carefully read this entire prospectus supplement and the accompanying prospectus, including the Risk Factors section of this prospectus supplement and the financial statements and the other information incorporated by reference into the accompanying prospectus, before making an investment decision.*

### Overview

We are a biopharmaceutical company seeking to develop and commercialize new drugs that work through a recently discovered system in cells known as RNA interference, or RNAi. We believe that drugs that work through RNAi, or RNAi therapeutics, have the potential to become a new major class of drugs, like small molecule, protein and antibody drugs. RNAi therapeutics could represent a fundamentally new way of treating disease because of their mechanism of action and, therefore, be used to address a broad range of unmet medical needs.

Our initial drug development programs are focused on products we call Direct[tm] RNAi therapeutics, because they will be administered directly to diseased parts of the body. In parallel, we are establishing capabilities for the development of products we call Systemic[tm] RNAi therapeutics, because they will travel through the blood stream to reach diseased parts of the body. We believe there are multiple opportunities for both Direct RNAi and Systemic RNAi therapeutics.

Our most advanced product candidate is ALN-RSV01, a Direct RNAi therapeutic for the treatment of lung infections caused by respiratory syncytial virus, or RSV. We initiated human clinical trials of ALN-RSV01 in December 2005. The next product candidate we expect to advance into clinical development will be for another lung infection, influenza, or flu. We expect to submit an investigational new drug application, or IND, for an RNAi therapeutic for pandemic flu as early as the end of 2006.

We also have discovery programs to develop Direct RNAi therapeutics for the treatment of the genetic respiratory disease known as cystic fibrosis; central nervous system disorders such as spinal cord injury, Parkinson s disease, Huntington s disease and neuropathic pain; ocular diseases such as age-related macular degeneration; and several other diseases that are the subject of collaborations with Merck & Co., Inc., or Merck, and Novartis Institutes for Biomedical Research, Inc., or Novartis.

Our main business strategy is to develop and commercialize a pipeline of proprietary RNAi therapeutic products and, in parallel, to form alliances with pharmaceutical companies to develop and commercialize a pipeline of partnered RNAi therapeutics. To date, we have formed such alliances with Merck, Novartis and Medtronic, Inc., or Medtronic.

### Background

RNAi is a recently discovered natural mechanism for selectively silencing genes, thereby blocking the production of specific proteins within cells. Our goal with RNAi therapeutics is to selectively silence genes whose protein products play harmful roles in disease. We expect that our RNAi therapeutics will consist of optimized small interfering RNAs, or siRNAs, designed to silence specific genes. siRNAs are the molecules within cells that directly trigger RNAi. Given that the nucleotide sequence of the entire human genome is now available, RNAi therapeutics can be designed, in theory, to silence any gene that encodes a protein involved in disease, even if this protein cannot be adequately controlled by conventional drugs. We therefore believe that RNAi therapeutics have the potential to become a broad new class of drugs that can block the production of disease-causing proteins through therapeutic gene silencing. To help realize this potential, we are developing a set of biological and chemical procedures that can be applied in a systematic way to develop RNAi therapeutics for a variety of diseases. These procedures and their systematic application comprise our product platform. We are using the current capabilities of our product platform to pursue development of a number of Direct RNAi therapeutics, and are working to enhance these capabilities to enable future development of Systemic RNAi therapeutics.

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**Product Programs**

*Respiratory Syncytial Virus*

Our most advanced product candidate, ALN-RSV01, is a Direct RNAi therapeutic for the treatment of RSV infection. RSV is highly contagious and infects nearly every child by the age of two years, causing respiratory tract infections severe enough to require hospitalization in over 100,000 cases each year in the United States. RSV infection also has significant consequences for the elderly and for other people with compromised immune systems. The only product currently approved for treating RSV infection, Virazole®(ribavirin), is approved only for limited indications and is very complex to administer. Another RSV product, Synagis®(palivizumab), which had sales of approximately $942 million in 2004, is approved for preventing severe lower respiratory tract infection in premature infants. Synagis is not approved for treating existing RSV infection in any patient population.

In our preclinical testing, ALN-RSV01 was shown to be an RSV-specific siRNA that is effective in both preventing and treating RSV infection in mice when administered intranasally, or through the nose. ALN-RSV01 also showed no significant toxicities in IND-enabling toxicology studies. We submitted an IND for intranasal ALN-RSV01 to the United States Food and Drug Administration, or FDA, in November 2005, and initiated Phase I clinical trials on this experimental drug in December 2005 in both the United States and Europe.

The ALN-RSV01 trial underway in the United States is expected to enroll 35 healthy adult volunteers, and to involve intranasal administration of drug or placebo in ascending single doses across five groups of volunteers. The second trial, underway in Europe, was designed to enroll 57 healthy adult volunteers divided into six groups. Three groups will receive drug or placebo intranasally in ascending single doses, while the other three groups will receive ascending multiple doses daily for five consecutive days. In each study, ALN-RSV01 will be evaluated for safety, tolerability and pharmacokinetics. We expect to have preliminary data available from these trials in the first half of 2006.

*Pandemic Flu*

An influenza pandemic is a global outbreak that occurs when a new flu virus appears in the human population, causes serious illness and spreads rapidly. World health authorities have expressed concern that an avian flu virus known as H5N1, which is believed to have led to human deaths in Southeast Asia and Turkey, could potentially mutate and cause a global pandemic. In this event, current options for preventing and treating influenza, such as vaccines and the drugs Tamiflu® and Relenza®, may not be adequate.

The focus of our pandemic flu program is to develop an RNAi therapeutic targeting gene sequences that are highly conserved across known flu viruses. We anticipate that these sequences would remain largely unchanged in any newly emerging flu virus, so that our RNAi therapeutic could be effective in preventing and treating infection by a pandemic virus. We expect that this RNAi therapeutic could be stockpiled by governments as part of their preparations for a flu pandemic. In December 2005, we were awarded initial funding for our pandemic flu program from DARPA, the Defense Advanced Research Projects Agency of the United States Department of Defense. We expect to submit an IND for a pandemic flu RNAi therapeutic as early as the end of 2006.

*Direct RNAi Discovery Programs*

In addition to our development efforts on RSV and pandemic flu, we are conducting research activities to discover Direct RNAi therapeutics to treat various diseases of the respiratory system, the central nervous system, or CNS, and the eye. The diseases for which we have discovery programs include:

*Cystic fibrosis*, or CF. CF is an inherited respiratory disorder caused by mutations in the gene for a protein known as the cystic fibrosis transmembrane conductance regulator, or CFTR. In most CF patients, potentially functional CFTR protein is produced but does not reach the cell surface. We are attempting to redirect this CFTR protein to the cell surface using siRNAs to silence specific genes involved in protein processing within the cell. We are conducting this work in collaboration with, and

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with funding from, Cystic Fibrosis Foundation Therapeutics, Inc., or CFFT, the drug discovery and development affiliate of the Cystic Fibrosis Foundation.

*Spinal cord injury*, or SCI. Our SCI program is focused on a cellular system known as the Nogo pathway that appears to play a key role in blocking the regeneration of nerves after injury. In collaboration with Merck, we are seeking to develop an RNAi therapeutic that inhibits this pathway, thereby allowing nerves to regenerate, and potentially reducing or preventing paralysis, after SCI.

*Huntington s disease*, or HD. HD is an inherited, progressive brain disease that results in uncontrolled movements, loss of intellectual faculties and emotional disturbance. HD patients produce an altered form of a protein known as huntingtin, whose presence is believed to trigger the death of important cells in the brain. In collaboration with Medtronic, we are seeking to develop an RNAi therapeutic that will protect these cells by suppressing production of huntingtin.

*Parkinson s disease*, or PD. PD is also a progressive brain disease characterized by uncontrollable tremors, and which may ultimately result in dementia. Like HD, PD is believed to result from the death of cells in the brain, in this case triggered by the presence of abnormally large amounts of a protein called alpha-synuclein. Our goal is to develop an RNAi therapeutic that will protect these cells by suppressing production of alpha-synuclein.

*Neuropathic pain.* Neuropathic pain is pain that originates in the nervous system and not as a result of any specific injury. A protein called sodium channel NaV1.8 is believed to play an important role in causing neuropathic pain. The goal of our program is to develop an RNAi therapeutic that will suppress the production of NaV1.8 and thereby alleviate neuropathic pain.

In addition to these programs, we have research activities seeking to discover Direct RNAi therapeutics directed to a number of other targets.

*Systemic RNAi and microRNA Technology Programs*

As we continue to build a pipeline of Direct RNAi therapeutics, we are also engaged in further optimization of RNAi technology to enable discovery and development of Systemic RNAi therapeutics. We have published some of our most important advances in peer-reviewed scientific journals. For example, in a November 2004 paper in *Nature*, we demonstrated that we could achieve therapeutic gene silencing in animals by intravenous injection of an siRNA that we had modified chemically to improve its drug-like properties. The siRNA featured in this work targeted the gene for a protein known as apolipoprotein B, or apoB, that is involved in cholesterol metabolism. Injection of our modified siRNA into animals led to significant reductions in the levels of both apoB and cholesterol in the bloodstream. We have subsequently extended these observations to show that the silencing of the apoB gene lasts for a number of days, and that it can protect animals on a high-fat diet against increases in blood cholesterol levels. We expect to publish additional research findings in the first half of 2006 relating to the activity of our systemically delivered siRNAs in non-human primates. We believe that we will be in a position to initiate development of Systemic RNAi therapeutics in the relatively near term.

In addition, we have adapted our technology to address the therapeutic possibilities offered by microRNAs, a recently discovered class of small RNAs that use the RNAi pathway to regulate genes and have been implicated in various human diseases. In animal experiments published in *Nature* in October 2005, we and our collaborators demonstrated that we could silence microRNAs using antagomirs, a potential new class of drugs we designed for this purpose. We expect that antagomirs may become an important component of our longer-term product platform for the development of RNAi therapeutics.

**Business Strategy**

Our business strategy is to develop and commercialize a pipeline of *proprietary* RNAi therapeutic products and, in parallel, to form alliances with pharmaceutical companies to develop and commercialize a pipeline of *partnered* RNAi therapeutics. For our proprietary RNAi therapeutic products, our aim is to develop these products to later stages of

clinical development and to commercialize them on our own or

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through alliances formed at these later stages. For our partnered RNAi therapeutic products, to date, we have formed four distinct discovery and development alliances with three separate companies: Merck, Medtronic and Novartis. Two of these alliances are with Merck, one focused on RNAi technology and RNAi therapeutics directed against Merck proprietary targets, the other focused on RNAi therapeutics for eye diseases. In these Merck alliances, we retain a major role in development and commercialization and a significant financial interest in each product. Our collaboration with Medtronic is focused on the development of novel drug-device products incorporating RNAi therapeutics to treat diseases caused by nerve degeneration. Our alliance with Novartis, formed in September 2005, is for the discovery, development and commercialization of RNAi therapeutics for a significant but defined number of targets in the Novartis research portfolio. In this alliance, we are eligible to receive substantial early funding in addition to future milestone and royalty payments. We are also eligible to receive additional payments if Novartis exercises a non-exclusive option to integrate our RNAi therapeutics platform into its internal efforts, in which case we would be eligible to receive future milestones and royalties on products resulting from those efforts.

One of the key factors in our ability to form significant alliances with pharmaceutical companies is the strength of our intellectual property position relating to the development and commercialization of siRNAs as therapeutics. This includes ownership of, or exclusive rights to, issued patents and pending patent applications claiming fundamental features of siRNAs and their use as therapeutics. These patents include those called Crooke, Kreutzer-Limmer and Glover. In addition, the United States Patent and Trademark Office recently issued notices of allowance for two patent applications in the Tuschl II patent series that broadly cover certain features for siRNAs that we believe are needed for their use as therapeutics. These allowed patent applications are exclusively licensed to Alnylam for therapeutic applications. Our patent estate also includes a broad portfolio of intellectual property relating to chemical modifications of siRNAs licensed from Isis Pharmaceuticals, Inc., or Isis, and a number of granted and pending patent applications claiming siRNAs directed to specific targets as treatments for particular diseases.

To realize additional value from our intellectual property, we also grant licenses to biotechnology companies in our InterfeRx$^{tm}$ program for the development and commercialization of RNAi therapeutics for specified targets in which we have no strategic interest. InterfeRx licensees include Nastech Pharmaceutical Company Inc. and GeneCare Research Institute Co., Ltd., while Benitec Ltd. has options to take InterfeRx licenses. We also license key aspects of our intellectual property to companies active in the research products and services market. To date, we have granted such licenses to 10 separate companies. Our InterfeRx and research product licenses aim to generate modest near-term revenues that we can re-invest in the development of our proprietary RNAi therapeutics pipeline.

We also seek funding for the development of our proprietary RNAi therapeutics pipeline from foundations and government sources. We have obtained funding for our cystic fibrosis program from CFFT. We have received a grant from the Michael J. Fox Foundation for our work on Parkinson s disease. Lastly, we have obtained initial government support for our pandemic flu program from DARPA.

Our principal executive office is located at 300 Third Street, Cambridge, Massachusetts 02142, and our telephone number is (617) 551-8200. Our internet address is 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. We have included our web site address as an inactive technical reference only.

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**THE OFFERING**

| | |
|---|---|
| Common stock offered | 5,115,961 |
| Common stock to be outstanding after this offering | 31,759,249 |
| Use of Proceeds | We estimate that the net proceeds from this offering will be approximately $62.3 million. We intend to use the net proceeds for general corporate purposes, including research and development expenses, clinical trial costs, general and administrative expenses and potential acquisitions of companies, products and technologies that complement our business. See Use of Proceeds. |
| Risk Factors | You should read the Risk Factors section of this prospectus supplement for a discussion of factors to consider before deciding to purchase shares of our common stock. |
| Nasdaq National Market Symbol | ALNY |

The number of shares of our common stock to be outstanding after this offering is based on 26,643,288 shares outstanding as of January 15, 2006.

The number of shares of our common stock to be outstanding after this offering excludes, as of January 15, 2006:

- 4,003,463 shares of common stock issuable upon the exercise of outstanding stock options at a weighted average exercise price of $5.93 per share;
- 52,630 shares of common stock issuable upon the exercise of outstanding warrants at a weighted average exercise price of $9.50 per share; and
- an aggregate of 2,116,118 additional shares of common stock reserved for future issuance under 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 underwriters of the option granted by us to purchase up to 767,394 additional shares of our common stock in this offering.

In accordance with the terms of our investor rights agreement with Novartis Pharma AG, in connection with this offering Novartis Pharma AG has the right to purchase from us up to 1,260,802 shares of our common stock and, if the option granted by us to the underwriters to purchase up to 767,394 additional shares is exercised in full, up to an additional 189,120 shares of our common stock, at a purchase price equal to the price that we sell shares in this offering if Novartis Pharma AG exercises its purchase right during the 30-day period after this offering, or at a purchase price that is a 10% premium to the price that we sell shares in this offering or 10% premium to the market price at the time of purchase, whichever is greater, if Novartis Pharma AG exercises its purchase right thereafter. The number of shares of our common stock to be outstanding after this offering excludes all of the shares that Novartis Pharma AG 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 Pharma AG will purchase, if any, in connection with this offering.

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## SUMMARY CONSOLIDATED FINANCIAL DATA

We derived the statement of operations data for the period from June 14, 2002 through December 31, 2002 and the years ended December 31, 2003 and 2004 from our consolidated financial statements, which have been audited by PricewaterhouseCoopers LLP, an independent registered public accounting firm. We derived the statement of operations data for the nine months ended September 30, 2005 and 2004 and the balance sheet data as of September 30, 2005 from our unaudited interim consolidated financial statements, which include, in the opinion of management, all adjustments, consisting only of normal recurring adjustments, necessary for a fair presentation of such data. Historical results are not necessarily indicative of future results. Operating results for the nine months ended September 30, 2005 are not necessarily indicative of the results that may be expected for the year ended December 31, 2005. You should read the data presented below in conjunction with Management s Discussion and Analysis of Financial Condition and Results of Operations and our financial statements and related footnotes incorporated by reference in this prospectus.

| | Nine Months Ended September 30, | | Year Ended December 31, | | Period from Inception (June 14, 2002) through December 31, 2002 |
|---|---|---|---|---|---|
| | 2005 | 2004 | 2004 | 2003 | |
| | (In thousands, except per share amounts) | | | | |
| **Statements of Operations Data:** | | | | | |
| **Net revenues from research collaborators** | $ 4,164 | $ 1,632 | $ 4,278 | $ 176 | $ |
| **Cost and expenses:** | | | | | |
| Research and development[1] | 22,557 | 19,425 | 24,603 | 13,097 | 3,342 |
| General and administrative[1] | 10,162 | 8,940 | 11,939 | 7,527 | 880 |
| Purchased in-process research and development | | | | 4,609 | |
| Total costs and expenses | 32,719 | 28,365 | 36,542 | 25,233 | 4,222 |
| Loss from operations | (28,555) | (26,733) | (32,264) | (25,057) | (4,222) |
| **Other income (expense):** | | | | | |
| Interest income | 759 | 296 | 504 | 179 | 86 |
| Interest expense | (717) | (480) | (661) | (127) | |
| Other income (expense) | 90 | (37) | (233) | (28) | |
| Total other income (expense) | 132 | (221) | (390) | 24 | 86 |
| Net loss | (28,423) | (26,954) | (32,654) | (25,033) | (4,136) |
| Accretion of redeemable convertible preferred stock | | (2,713) | (2,713) | (2,906) | (748) |

| | | | | | |
|---|---|---|---|---|---|
| Net loss attributable to common stockholders | $ (28,423) | $ (29,667) | $ (35,367) | $ (27,939) | $ (4,884) |
| Net loss per common share basic and diluted | $ (1.37) | $ (3.14) | $ (2.98) | $ (29.64) | $ (14.74) |
| Weighted average common shares used to compute basic and diluted net loss per common share | 20,674 | 9,436 | 11,886 | 943 | 331 |

(1) Non-cash stock-based compensation expense included in these amounts are as follows:

| | | | | | |
|---|---|---|---|---|---|
| Research and development | $ 1,815 | $ 1,395 | $ 2,087 | $ 2,832 | $ 172 |
| General and administrative | 1,780 | 1,520 | 2,019 | 623 | |
| Total non-cash stock-based compensation | $ 3,595 | $ 2,915 | $ 4,106 | $ 3,455 | $ 172 |

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The following table sets forth our balance sheet data at September 30, 2005 on an actual basis and on an as adjusted basis to give effect to the sale of 5,115,961 shares of common stock in this offering at the price to public of $13.00 per share, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

| | As of September 30, 2005 | |
|---|---|---|
| | Actual | As Adjusted |
| | ($ in thousands) (unaudited) | |
| **Consolidated Balance Sheet Data:** | | |
| Cash, cash equivalents and marketable securities | $ 24,809 | $ 87,081 |
| Working capital | 18,695 | 80,967 |
| Total assets | 43,248 | 105,520 |
| Note payable, net of current portion | 5,782 | 5,782 |
| Total stockholders equity | 23,071 | 85,343 |

The actual amounts as of September 30, 2005 in the preceding table do not include the approximately $68.5 million of proceeds from the Novartis alliance that we received in October 2005. After giving effect to the receipt of a $10 million upfront payment and approximately $58.5 million related to the purchase by Novartis of 5,267,865 shares of our common stock, cash, cash equivalents and marketable securities would have been approximately $93.3 million, working capital would have been approximately $87.2 million, total assets would have been approximately $111.8 million and total stockholders equity would have been approximately $75.2 million.

In the event that Novartis Pharma AG purchases all of the shares of common stock that it has the right to purchase from us in connection with this offering, each of the as adjusted cash, cash equivalents and marketable securities, as adjusted working capital, as adjusted total assets and as adjusted total stockholders equity in the preceding table would increase by approximately $16.4 million, and if the option granted by us to the underwriters to purchase additional shares is exercised in full, by an additional approximately $2.5 million.

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## RISK FACTORS

*An investment in our common stock involves a high degree of risk. In deciding whether to invest, you should carefully consider the following risk factors, as well as the other information contained in this prospectus supplement. 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.*

### Risks Related to Our Business

### Risks Related to Being an Early Stage Company

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

Our operations began in June 2002 and we have only a limited operating history upon which you can evaluate our business and prospects. In addition, as an early stage company, we have limited experience and have not yet demonstrated an ability to successfully overcome many of the risks and uncertainties frequently encountered by companies in new and rapidly evolving fields, particularly in the biopharmaceutical area. For example, to execute our business plan, we will need to successfully:

- execute product development activities using an unproven technology;
- build and maintain a strong intellectual property portfolio;
- gain acceptance for the development and commercialization of our products;
- develop and maintain successful strategic relationships; 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, raise capital, expand our business or continue our operations.

***The approach we are taking to discover and develop novel drugs 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 RNAi technology. Neither we nor any other company has received regulatory approval to market therapeutics utilizing siRNAs, the class of molecule we are trying to develop into drugs. The scientific discoveries that form the basis for our efforts to discover and develop new drugs are relatively new. The scientific evidence to support the feasibility of developing drugs based on these discoveries is both preliminary and limited. Skepticism as to the feasibility of developing RNAi therapeutics has been expressed in scientific literature. For example, there are potential challenges to achieving safe RNAi therapeutics based on the so-called off-target effects and activation of the interferon response. There are also potential challenges to achieving effective RNAi therapeutics based on the need to achieve efficient delivery into cells and tissues in a clinically relevant manner and at doses that are cost-effective.

Very few drug candidates based on these discoveries have ever been tested in animals or humans. siRNAs do 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

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ways. As a result, we may never succeed in developing a marketable product. If we do not successfully develop and commercialize drugs based upon our technological approach, we will not become profitable and the value of our common stock will decline.

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

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

***We have a history of losses and may never be profitable.***

We have experienced significant operating losses since our inception. As of September 30, 2005, we had an accumulated deficit of $91.4 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 as we expand our efforts to discover, develop and commercialize RNAi therapeutics. We anticipate that the majority of any revenue we generate over the next several years will be from collaborations with pharmaceutical companies, but cannot be certain that we will be able to secure or maintain these collaborations or to meet the obligations or achieve any milestones that we may be required to meet or achieve to receive payments. If we are unable to earn revenue from collaborations, we may be unable to continue our efforts to discover, develop and commercialize RNAi therapeutics without raising financing from other sources.

To become and remain profitable, we must succeed in developing and commercializing novel drugs with significant market potential. This will require us to be successful in a range of challenging activities, including preclinical 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 profitable, the market price of our common stock could decline. In addition, we may be unable to raise capital, expand our business, diversify our product offerings or continue our operations.

***We will require substantial additional funds to complete our research and development activities and if additional funds are not available we may need to 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 preclinical testing and clinical trials of any product candidates, and to manufacture and market any products that are approved for commercial sale. Because the successful development of our products is uncertain, we are unable to estimate the actual funds we will require to develop and commercialize them.

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

- our progress in our preclinical and clinical trials;
- our progress in demonstrating that siRNAs can be active as drugs;
- our ability to develop relatively standard procedures for selecting and modifying siRNA drug candidates;
- progress in our research and development programs, as well as the magnitude of these programs;
- the timing, receipt, and amount of milestone and other payments, if any, from present and future collaborators, if any;

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our ability to establish and maintain additional collaborative arrangements;

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

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

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

We will be required to seek additional funding in the future and intend to do so through either collaborative arrangements, public or private equity offerings or debt financings, or a combination of one or more of these funding sources. Additional funds may not be available to us on acceptable terms or at all. In addition, the terms of any financing may adversely affect the holdings or the rights of our stockholders. For example, if we raise additional funds by issuing equity securities, further dilution to our stockholders will result. In addition, our investor rights agreement with Novartis Pharma AG provides Novartis Pharma AG with the right generally to maintain its ownership percentage in Alnylam. While the exercise of this right may provide us with additional funding under some circumstances, the exercise of this right will also cause further dilution to our stockholders. Debt financing, if available, may involve restrictive covenants that could limit our flexibility in conducting future business activities. If we are unable to obtain funding on a timely basis, we may be required to significantly curtail one or more of our research or development programs. We also could be required to seek funds through arrangements with collaborators or others that may require us to relinquish rights to some of our technologies, product candidates or products that we would otherwise pursue on our own.

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

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

In October 2005, we entered into a collaboration agreement with Novartis. Under this agreement, Novartis will select disease targets toward which the parties will collaborate to develop drug candidates. Novartis will reimburse us for the costs we incur to develop these drug candidates and Novartis will commercialize and market any products derived from this collaboration. In addition, Novartis will pay us certain pre-determined amounts based on the achievement of pre-clinical and clinical milestones as well as royalties on the annual net sales of any products derived from this collaboration. This collaboration has an initial term of three years that may be extended by Novartis for two additional one-year terms. Novartis may elect to terminate this collaboration after two years under some circumstances and either party may terminate this collaboration in the event of a material uncured breach by the other party. We expect that a substantial amount of the funding for our operations will come from this collaboration. If this collaboration is unsuccessful, or if it is terminated, our business could be adversely affected.

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

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

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first offer may make it difficult for us to form future alliances with other parties, which could impair development of our own products. If we are unable to develop products independent of Novartis, our business could be adversely affected.

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

We do not have any capability for sales, marketing or distribution and have limited capabilities for drug development. Accordingly, we have entered into alliances with other companies that can provide such capabilities and may need to enter into additional alliances in the future. For example, we may enter into alliances with major pharmaceutical companies to jointly develop specific drug candidates and to jointly commercialize them if they are approved. In such alliances, we would expect our pharmaceutical collaborators to provide substantial capabilities in clinical development, regulatory affairs, marketing and sales. We may not be successful in entering into any such alliances on favorable terms due to various factors including Novartis right of first offer. Even if we do succeed in securing such alliances, we may not be able to maintain them if, for example, development or approval of a drug candidate is delayed or sales of an approved drug are disappointing. Furthermore, any delay in entering into collaboration agreements could delay the development and commercialization of our drug candidates and reduce their competitiveness even if they reach the market. Any such delay related to our collaborations could adversely affect our business.

We entered into a collaboration agreement with Merck in September 2003, under which Merck may elect to pay a portion of the costs to develop and market certain drug candidates that we may initially develop based on information and materials provided by Merck. Merck is under no obligation to pay any of the development and commercialization costs for any of these drug candidates, and it may elect not to do so. For drug candidates from our Merck collaboration that Merck does not elect to fund, and for drug candidates we may develop outside of this collaboration, we have formed additional collaborations to fund all or part of the costs of drug development and commercialization, such as our collaboration with Novartis, the second collaboration and license agreement we entered into with Merck for ocular disease as well as collaborations with Medtronic and the CFFT. We may not, however, be able to enter into additional collaborations, and the terms of any collaboration agreement we do secure may not be favorable to us. If we are not successful in our efforts to enter into future collaboration arrangements with respect to a particular drug candidate, we may not have sufficient funds to develop this or any other drug candidate internally, or to bring any drug candidates to market. If we do not have sufficient funds to develop and bring our drug candidates to market, we will not be able to generate sales revenues from these drug candidates, and this will substantially harm our business.

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

Our dependence on collaborators for capabilities and funding means that our business would 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. If a collaborator terminates its collaboration with us, for breach or otherwise, it would be difficult for us to attract new collaborators and could

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adversely affect how we are perceived in the business and financial communities. In addition, a collaborator could determine that it is in its financial interest to:

- pursue alternative technologies or develop alternative products, either on its own or jointly with others, that may be competitive with the products on which it is collaborating with us or which could affect its commitment to the collaboration with us;

- pursue higher-priority programs or change the focus of its development programs, which could affect the collaborator s commitment to us; or

- if it has marketing rights, choose to devote fewer resources to the marketing of our product candidates, if any are approved for marketing, than it does for product candidates of its own development.

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

***We 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-GMP material for use in *in vitro* and *in vivo* experiments. In order to develop products, apply for regulatory approvals and commercialize our products, we will need to develop, contract for, or otherwise arrange for the necessary manufacturing capabilities. We may manufacture clinical trial materials ourselves or we may rely on others to manufacture the materials we will require for any clinical trials that we initiate. Only a limited number of manufacturers supply synthetic RNAi. We have contracted with Dowpharma, a division of The Dow Chemical Company, for supply of material to meet our testing needs for toxicology and clinical testing. There are risks inherent in pharmaceutical manufacturing that could affect Dowpharma s ability to meet our delivery time requirements or provide adequate amounts of material to meet our needs. Included in these risks are synthesis failures and contamination during the manufacturing process, both of which could result in unusable product and cause delays in our development process. The manufacturing process for any products that we may develop is an element of the FDA approval process and we will need to contract with manufacturers who can meet the FDA 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 collaborators, to produce materials required for commercial production. We may experience difficulty in obtaining adequate manufacturing capacity for our needs. If we are unable to obtain or maintain contract manufacturing for these product candidates, or to do so on commercially reasonable terms, we may not be able to successfully develop and commercialize our products.

To the extent that we enter into manufacturing arrangements with third parties, we will depend on these third parties to perform their obligations in a timely manner and consistent with regulatory requirements. The failure of a third-party manufacturer to perform its obligations as expected could adversely affect our business in a number of ways, including:

- we may not be able to initiate or continue clinical trials of products that are under development;

- we may be delayed in submitting applications for regulatory approvals for our products;

- we may lose the cooperation of our collaborators;

- we may be required to cease distribution or recall some or all batches of our products; and

- ultimately, we may not be able to meet commercial demands for our products.

If a third-party manufacturer with whom we contract fails to perform its obligations, we may be forced to manufacture the materials ourselves, for which we may not have the capabilities or resources, or enter into an

agreement with a different third-party manufacturer, which we may not be able to do with reasonable terms, if at all. In addition, if we are required to change manufacturers for any reason, we will be required to verify that

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the new manufacturer maintains facilities and procedures that comply with quality standards and with all applicable regulations and guidelines. The delays associated with the verification of a new manufacturer could negatively affect our ability to develop product candidates in a timely manner or within budget. Furthermore, a manufacturer may possess technology related to the manufacture of our product candidate that such manufacturer owns independently. This would increase our reliance on such manufacturer or require us to obtain a license from such manufacturer in order to have another third party manufacture our products.

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

We have no sales, marketing or distribution experience. We expect to rely heavily on third parties to launch and market certain of our product candidates, if approved. We may have limited or no control over the sales, marketing and distribution activities of these third parties. Our future revenues may depend heavily on the success of the efforts of these third parties.

To develop internal sales, distribution and marketing capabilities, we will have to invest significant amounts of financial and management resources. For products where we decide to perform sales, marketing and distribution functions ourselves, we could face a number of additional risks, including:

we may not be able to attract and build a significant marketing or sales force;

the cost of establishing a marketing or sales force may not be justifiable in light of the revenues generated by any particular product; and

our direct sales and marketing efforts may not be successful.

**Risks Related to Managing Our Operations**

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

We are highly dependent upon our senior management and scientific staff. The loss of the service of any of the members of our senior management, including Dr. John Maraganore, our President and 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 key employees.

Although we have generally been successful in our recruiting efforts, we face intense competition for qualified individuals from numerous pharmaceutical and biotechnology companies, universities, governmental entities and other research institutions. We may be unable to attract and retain suitably qualified individuals, and our failure to do so could have an adverse effect on our ability to implement our business plan.

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

Since we commenced operations in 2002, we have grown rapidly to over 90 full time equivalent employees, with offices and laboratory space in both Cambridge, Massachusetts and Kulmbach, Germany. This rapid and substantial growth, and the geographical separation of our sites, has placed a strain on our administrative and operational infrastructure, and we anticipate that our continued growth will have a similar impact. If drug candidates we develop enter and advance through clinical trials, we will need to expand our development, regulatory, manufacturing, marketing and sales capabilities or contract with other organizations to provide these capabilities for us. As our operations expand, we expect that we will need to manage additional relationships with various collaborators, suppliers and other organizations. Our ability to manage our operations and growth will require us to continue to improve our operational, financial and management controls, reporting systems and procedures in at least two different countries. 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.

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***If we are unable to manage the challenges associated with our international operations, the growth of our business could be limited.***

In addition to our operations in Cambridge, Massachusetts, we operate an office and laboratory in Kulmbach, Germany. We are subject to a number of risks and challenges that specifically relate to these international operations. Our international operations may not be successful if we are unable to meet and overcome these challenges, which could limit the growth of our business and may have an adverse effect on our business and operating results. These risks include:

- fluctuations in foreign currency exchange rates that may increase the U.S. dollar cost of our international operations;
- difficulty managing operations in multiple locations, which could adversely affect the progress of our product candidate development program and business prospects;
- local regulations that may restrict or impair our ability to conduct biotechnology-based research and development;
- foreign protectionist laws and business practices that favor local competition; and
- failure of local laws to provide the same degree of protection against infringement of our intellectual property, which could adversely affect our ability to develop product candidates or reduce future product or royalty revenues, if any, from product candidates we may develop.

## Risks Related to Our Industry

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

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

Preclinical testing and clinical trials of new drug candidates are lengthy and expensive and the historical failure rate for drug candidates is high. We currently have one product candidate in Phase I clinical trials which we call ALN-RSV01, for the treatment of RSV infection. We may not be able to advance any further product candidates into clinical trials. The results from preclinical testing of a drug candidate may not predict the results that will be obtained in human clinical trials. We, the FDA or other applicable regulatory authorities may suspend clinical trials of a drug candidate at any time if we or they believe the subjects or patients participating in such trials are being exposed to unacceptable health risks, or for other reasons. Among other reasons, adverse side effects of a drug candidate on subjects or patients in a clinical trial could result in the FDA or foreign regulatory authorities suspending or terminating the trial and refusing to approve a particular drug candidate for any or all indications of use.

Clinical trials of a new drug candidate require the enrollment of a sufficient number of patients, including patients who are suffering from the disease the drug candidate is intended to treat and who meet other eligibility criteria. Rates of patient enrollment are affected by many factors, including the size of the patient population, the nature of the protocol, the proximity of patients to clinical sites, the availability of effective treatments for the relevant disease and the eligibility criteria for the clinical trial. Delays in patient enrollment can result in increased costs and longer development times.

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

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

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

- discussions with the FDA or comparable foreign authorities regarding the scope or design of our clinical trials;
- problems in engaging IRBs to oversee trials or problems in obtaining IRB approval of studies;
- delays in enrolling patients and volunteers into clinical trials;
- high drop-out rates for patients and volunteers in clinical trials;
- negative results of clinical trials;
- inadequate supply or quality of drug candidate materials or other materials necessary for the conduct of our clinical trials;
- serious and unexpected drug-related side effects experienced by participants in our clinical trials; or
- unfavorable FDA inspection and review of a clinical trial site or records of any clinical or preclinical investigation.

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

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

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

Our drug candidates are subject to extensive governmental regulations relating to development, clinical trials, manufacturing and commercialization. Rigorous preclinical testing and clinical trials and an extensive regulatory approval process are required to be successfully completed in the United States and in many foreign

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jurisdictions before a new drug can be sold. Satisfaction of these and other regulatory requirements is costly, time consuming, uncertain and subject to unanticipated delays. It is possible that none of the drug candidates we may develop will obtain the appropriate regulatory approvals necessary for us or our collaborators to begin selling them.

We have very little 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 exceeds five years following the commencement of clinical trials, depending upon the complexity of the drug candidate. Any analysis we perform of data from preclinical 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. Under federal law, new drug applications are subject to substantial application user fees, currently exceeding $767,000, and the sponsor of an approved new drug application is also subject to annual product and establishment user fees, currently exceeding $42,000 per product and $264,000 per establishment, each of which is typically increased annually.

Because the drugs we are intending to develop may represent a new class of drug, the FDA has not yet established any definitive policies, practices or guidelines in relation to these drugs. While we expect any RSV, PD, SCI, CF or pandemic flu product candidates we develop will be regulated as a new drug under the Federal Food, Drug, and Cosmetic Act, the FDA could decide to regulate them or other products we may develop as biologics under the Public Health Service Act. The lack of policies, practices or guidelines may hinder or slow review by the FDA of any regulatory filings that we may submit. Moreover, the FDA may respond to these submissions by defining requirements we may not have anticipated. Such responses could lead to significant delays in the clinical development of our product candidates. In addition, because there are approved treatments for RSV and PD, in order to receive regulatory approval, we will need to demonstrate through clinical trials that the product candidates we develop to treat these diseases, if any, are not only safe and effective, but safer or more effective than existing products.

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

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

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

Before obtaining regulatory approval for the sale of our drug candidates, we must conduct, at our own expense, extensive preclinical tests and clinical trials to demonstrate the safety and efficacy in humans of our drug candidates. Preclinical and clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. Success in preclinical testing and early clinical trials does not ensure that later clinical trials will be successful, and interim results of a clinical trial do not necessarily predict final results.

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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, preclinical testing and the clinical trial process that could delay or prevent our ability to receive regulatory approval or commercialize our drug candidates, including:

- regulators or IRBs may not authorize us to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- our preclinical tests or clinical trials may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional preclinical testing or clinical trials or we may abandon projects that we expect to be promising;
- enrollment in our clinical trials may be slower than we currently anticipate or participants may drop out of our clinical trials at a higher rate than we currently anticipate, resulting in significant delays;
- our third party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner;
- we might have to suspend or terminate our clinical trials if the participants are being exposed to unacceptable health risks;
- regulators or IRBs may require that we hold, suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements;
- the cost of our clinical trials may be greater than we anticipate;
- the supply or quality of our drug candidates or other materials necessary to conduct our clinical trials may be insufficient or inadequate; and
- the effects of our drug candidates may not be the desired effects or may include undesirable side effects or the drug candidates may have other unexpected characteristics.

***Even if we obtain regulatory approvals, our marketed drugs will be subject to ongoing regulatory review. If we fail to comply with continuing United States and foreign regulations, we could lose our approvals to market drugs and our business would be seriously harmed.***

Following any initial regulatory approval of any drugs we may develop, we will also be subject to continuing regulatory review, including the review of adverse drug experiences and clinical results that are reported after our drug products are made commercially available. This would include results from any post-marketing tests or vigilance required as a condition of approval. The manufacturer and manufacturing facilities we use to make any of our drug candidates will also be subject to periodic review and inspection by the FDA. The discovery of any previously unknown problems with the product, manufacturer or facility may result in restrictions on the drug or manufacturer or facility, including withdrawal of the drug from the market. We do not have, and currently do not intend to develop, the ability to manufacture material for our clinical trials or on a commercial scale. We may manufacture clinical trial materials or we may contract a third-party to manufacture these materials for us. Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured products ourselves, including reliance on the third-party manufacturer for regulatory compliance. Our product promotion and advertising is also subject to regulatory requirements and continuing FDA review.

If we fail to comply with applicable continuing regulatory requirements, we may be subject to fines, suspension or withdrawal of regulatory approval, product recalls and seizures, operating restrictions and criminal prosecutions.

***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

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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 products.

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

- the timing of our receipt of any marketing approvals, the terms of any approvals and the countries in which approvals are obtained;
- the safety, efficacy and ease of administration;
- the willingness of patients to accept relatively new routes of administration;
- the success of our physician education programs;
- the availability of government and third-party payor reimbursement;
- the pricing of our products, particularly as compared to alternative treatments; and
- the availability of alternative effective treatments for the diseases that product candidates we develop are intended to treat.

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

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

- warning letters;
- recalls or public notification or medical product safety alerts;
- restrictions on, or prohibitions against, marketing our products;
- restrictions on importation of our products;
- suspension of review or refusal to approve pending applications;
- 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.

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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 and the 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 challenging the prices charged for medical products. If the price we are able to charge for any products we develop is inadequate in light of our development and other costs, our profitability could be adversely affected.

We currently expect that any drugs we develop may need to be administered under the supervision of a physician. Under currently applicable law, drugs that are not usually self-administered may be eligible for coverage by the Medicare program if:

- they are incident to a physician s services;
- they are reasonable and necessary for the diagnosis or treatment of the illness or injury for which they are administered according to accepted standard of medical practice;
- they are not excluded as immunizations; and
- they have been approved by the FDA.

There may be significant delays in obtaining coverage for newly-approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the FDA. Moreover, eligibility for coverage does not imply that any drug will be reimbursed in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim payments for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement may be based on payments allowed for lower-cost drugs that are already reimbursed, may be incorporated into existing payments for other services and may reflect budgetary constraints or imperfections in Medicare data. Net prices for drugs may be reduced by mandatory discounts or rebates required by government health care programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Third party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement rates. Our inability to promptly obtain coverage and profitable reimbursement rates from both government-funded and private payors for new drugs that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products, and our overall financial condition.

We believe that the efforts of governments and third-party payors to contain or reduce the cost of healthcare will continue to affect the business and financial condition of pharmaceutical and biopharmaceutical companies. A number of legislative and regulatory proposals to change the healthcare system in the United States and other major healthcare markets have been proposed in recent years. These proposals have included prescription drug benefit legislation recently enacted in the United States and healthcare reform legislation recently enacted by certain states. Further federal and state legislative and regulatory developments are possible and we expect ongoing initiatives in the United States to increase pressure on drug pricing. Such reforms could have an adverse effect on anticipated revenues from drug candidates that we may successfully develop.

Another development that may affect the pricing of drugs is Congressional action regarding drug reimportation into the United States. The Medicare Prescription Drug Plan legislation, which became law in December 2003, requires the Secretary of Health and Human Services to promulgate regulations for drug reimportation from Canada into the United States under some circumstances, including when the drugs are sold at a lower price than in the United States. The Secretary retains the discretion not to implement a drug reimportation plan if he finds that the benefits do not outweigh the cost. Proponents of drug reimportation may attempt to pass legislation that would directly allow

reimportation under certain circumstances. If legislation

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or regulations were passed allowing the reimportation of drugs, they could decrease the price we receive for any products that we may develop, negatively affecting our anticipated revenues and prospects for profitability.

Some states and localities have established drug importation programs for their citizens. So far, these programs have not led to a large proportion of prescription orders to be placed for foreign purchase. The FDA has warned that importing drugs is illegal and in December 2004 began to take action to halt the use of these programs by filing a civil complaint against an importer of foreign prescription drugs. If such programs were to become more substantial and were not to be encumbered by the federal government, they could also decrease the price we receive for any products that we may develop, negatively affecting our anticipated revenues and prospects for profitability.

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

Our business exposes us to significant potential product liability risks that are inherent in the development, manufacturing and marketing of human therapeutic products. Product liability claims could delay or prevent completion of our clinical development programs. If we succeed in marketing products, such claims could result in an FDA investigation of the safety and effectiveness of our products, our manufacturing processes and facilities or our marketing programs, and potentially a recall of our products or more serious enforcement action, or limitations on the indications for which they may be used, or suspension or withdrawal of approval. We currently have product liability insurance at a level that we believe is appropriate for our stage of development but we will likely need to obtain higher levels prior to marketing any of our drug candidates. Any insurance we obtain may not provide sufficient coverage against potential liabilities. Furthermore, clinical trial and product liability insurance is becoming increasingly expensive. As a result, we may be unable to obtain sufficient insurance at a reasonable cost to protect us against losses caused by product liability claims that could have a material adverse effect on our business.

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

Our research and development involves the use of hazardous materials, chemicals and various radioactive compounds. We maintain quantities of various flammable and toxic chemicals in our facilities in Cambridge and Germany that are required for our research and development activities. We believe our procedures for storing, handling and disposing these materials in our Cambridge facility comply with the relevant guidelines of the City of Cambridge and the Commonwealth of Massachusetts and the procedures we employ in our German facility comply with the standards mandated by applicable German laws and guidelines. Although we believe that our safety procedures for handling and disposing of these materials comply with the standards mandated by applicable regulations, the risk of accidental contamination or injury from these materials cannot be eliminated. If an accident occurs, we could be held liable for resulting damages, which could be substantial. We are also subject to numerous environmental, health and workplace safety laws and regulations, including those governing laboratory procedures, exposure to blood-borne pathogens and the handling of biohazardous materials.

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

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**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 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 preclinical testing, conducting clinical trials, obtaining regulatory approvals, and in manufacturing and marketing pharmaceutical products;
- product candidates that are based on previously tested or accepted technologies;
- products that have been approved or are in late stages of development; and
- collaborative arrangements in our target markets with leading companies and research institutions.

We will face intense competition from drugs that have already been approved and accepted by the medical community for the treatment of the conditions for which we may develop drugs. We also expect to face competition from new drugs that enter the market. We believe a significant number of drugs are currently under development, and may become commercially available in the future, for the treatment of conditions for which we may try to develop drugs. For instance, we are currently evaluating RNAi therapeutics for RSV, PD and CF. Virazole is currently marketed for the treatment of certain RSV patients, numerous drugs are currently marketed for the treatment of PD and two drugs, TOBI and Pulmozyme, are currently marketed for the treatment of CF. These drugs, or other of our competitors products, may be more effective, or marketed and sold more effectively, than any products we develop.

If we successfully develop drug candidates, and obtain approval for them, we will face competition based on many different factors, including:

- the safety and effectiveness of our products;
- the ease with which our products can be administered and the extent to which patients accept relatively new routes of administration;
- the timing and scope of regulatory approvals for these products;
- the availability and cost of manufacturing, marketing and sales capabilities;
- price;
- reimbursement coverage; and
- patent position.

Our competitors may develop or commercialize products with significant advantages over any products we develop based on any of the factors listed above or on other factors. Our competitors may therefore be more successful in commercializing their products than we are, which could adversely affect our competitive position and business. Competitive products may make any products we develop obsolete or noncompetitive before we can recover the expenses of developing and commercializing our drug candidates. Furthermore, we also face competition from existing and new treatment methods that reduce or eliminate the need for drugs, such as the use of advanced medical

devices. The development of new medical devices or other treatment methods for the diseases we are targeting could make our drug candidates noncompetitive, obsolete or uneconomical.

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

In addition to the competition we face from competing drugs in general, we also face competition from other companies working to develop novel drugs using technology that competes more directly with our own. We are aware of several other companies that are working in the field of RNAi, including Sirna Therapeutics, Inc., Acuity Pharmaceuticals, Inc., Nucleonics, Inc., SR Pharma and CytRx Corporation. In addition, we granted licenses to Isis, GeneCare Research Institute Co., Ltd., Benitec Ltd., Nastech Pharmaceutical Company Inc. as well as 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.

We also compete with companies working to develop antisense-based drugs. Like RNAi product candidates, antisense drugs target mRNAs in order to suppress the activity of specific genes. Isis is currently marketing an antisense drug and has several antisense drug candidates in clinical trials, and another company, Genta Inc., has multiple antisense drug candidates in late-stage 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.

**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 United States patent applications are confidential until patents issue, such as applications filed prior to November 29, 2000, or applications filed after such date which will not be filed in foreign countries, third parties may have filed patent applications for technology covered by our pending patent applications without our being aware of those applications, and our patent applications may not have priority over those applications. For this and other reasons, we may be unable to secure desired patent rights, thereby losing desired exclusivity. Further, we may be required to obtain licenses under third-party patents to market our proposed products or conduct our research and development or other activities. If licenses are not available to us on acceptable terms, we will not be able to market the affected products or conduct the desired activities.

Our strategy depends on our ability to rapidly identify and seek patent protection for our discoveries. In addition, we will 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. The mere issuance of a patent does not guarantee that it is valid or enforceable, so even if we obtain patents, they may not be valid or enforceable against third parties.

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 United States Patent and Trademark Office and its foreign counterparts use to grant patents are not always applied predictably or uniformly and can change. 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.

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

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

We are a party to a number of licenses that give us rights to third party intellectual property that is necessary or useful for our business. In particular, we have obtained licenses from Isis, Hybridon, Carnegie Institution of Washington, Cancer Research Technology Limited, the Massachusetts Institute of Technology, the Whitehead Institute, Garching Innovation GmbH, representing the Max Planck Gesellschaft zur Förderung der Wissenschaften e.V., referred to as the Max Planck organization, Stanford University, Cold Spring Harbor Laboratory and the University of South Alabama. 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.

***Two patents from one of our key patent families, the so-called Kreutzer-Limmer patent series of patents, are the subjects of opposition proceedings in the European Patent Office and the Australian Patent Office, which could result in the invalidation of these patents.***

A German Utility Model covering RNAi composition was registered in 2003, and a patent covering RNAi compositions and their use was granted by the European Patent Office, or EPO, in 2002, in South Africa in 2003 and accepted for grant in Australia in 2004. Related patent applications are pending in other countries, including the United States. A German Utility Model is a form of patent that is directed only to physical matter, such as medicines, and does not cover methods. The maximum period of protection afforded by the German Utility Model ends in 2010. After the grant by the EPO of the Kreutzer-Limmer patent, published under publication number EP 1144623B9, several oppositions to the issuance of the European patent were filed with the EPO, a practice that is allowed under the European Patent Convention. Each of the oppositions raises a number of grounds for the invalidation of the patent, including the use of disclaimer practice. The EPO opposition division in charge of the opposition proceedings may agree with one or more of the grounds and could revoke the patent in whole or restrict the scope of the claims. In June 2005, the EPO granted us a new patent covering short interfering RNAs, or siRNAs, including therapeutic compositions, methods and uses of siRNAs and derivatives with a length between 15 and 49 nucleotides. The notification grant of this patent was published on June 8, 2005 under publication number EP 1214945. However, this patent may also become the subject of opposition, which could result in its invalidation. It may be several years before the outcome of any opposition proceeding is decided by the EPO.

In addition, the Enlarged Board of Appeal at the EPO rendered a decision in an unrelated case covering what is known as disclaimer practice . With a disclaimer, a patent applicant gives up, or disclaims, part of the originally claimed invention in a patent application in order to overcome prior art and adds a limitation to the claims which may have no basis in the original disclosure. The Enlarged Board determined that disclaimer practice is allowed under the European Patent Convention under a defined set of circumstances. It now has to be determined as part of the opposition proceedings regarding the Kreutzer-Limmer patent whether a certain limitation introduced during the prosecution of EP 1155623 represents a disclaimer and, if so, whether the use of a disclaimer during the prosecution of this case falls within one of the allowable circumstances. Determination by the EPO opposition division that the use of the disclaimer in this case does not fall under

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one of the allowed circumstances could result in the invalidation of the Kreutzer-Limmer patent. Even if the EPO opposition division determines that the use of a disclaimer is permissible, the Kreutzer-Limmer patent would remain subject to the other issues raised in the opposition. If the Kreutzer-Limmer patent is invalidated or limited for any reason, other companies will be better able to develop products that compete with ours, which could adversely affect our competitive business position, business prospects and financial condition.

Furthermore, one party has given notice to the Australian Patent Office, IP Australia, on March 9, 2005, that it opposes the grant of AU 778474. This Australian patent derives from the same parent international patent application that gave rise to EP 1144623B9, and is of similar, but not the same, scope. In particular, its claims do not rely upon a disclaimer. The opposing party recently furnished the grounds for its opposition, and has until March 9, 2006, to submit documents in support of the stated grounds. Like the proceedings in the EPO, these proceedings may take several years before an outcome becomes final.

***The Notices of Allowance announced for the so-called Tuschl II patent application series may not result in the issuance of United States patents or any patents that issue could be found invalid by a United States Court.***

On January 17, 2006 and on January 24, 2006, we announced that the United States Patent and Trademark Office, or USPTO, has allowed claims in two patent applications that broadly cover methods for preparing siRNAs, the molecules that mediate RNAi. The USPTO issued a Notice of Allowance for patent applications 10/832,248 and 10/832,432 in the Tuschl II patent series. Following a Notice of Allowance , the final issuance of a patent involves several administrative steps that typically are completed within three months. However, there is a risk that the USPTO could decide to re-open prosecution of the allowed patent applications, which could result in patents not issuing from these applications.

Additionally, after a patent is issued, third parties can challenge the validity and/or enforceability of the patent. If patents issue from these applications, a subsequent United States court of law may find the patents either invalid or unenforceable.

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

RNA interference is a relatively new scientific field that has generated many different patent applications from organizations and individuals seeking to obtain important patents in the field. These applications claim many different methods, compositions and processes relating to the discovery, development and commercialization of RNAi therapeutics. Because the field is so new, very few of these patent applications have been fully processed by government patent offices around the world, and there is a great deal of uncertainty about which patents will issue, when, to whom, and with what claims. It is likely that there will be significant litigation and other proceedings, such as interference and opposition proceedings in various patent offices, relating to patent rights in the RNAi field. Others may attempt to invalidate our intellectual property rights. Even if our rights are not directly challenged, disputes among third parties could lead to the weakening or invalidation of our intellectual property rights.

In addition, there are many issued and pending patents that claim aspects of oligonucleotide chemistry that we may need to apply to our siRNA drug candidates. There are also many issued patents that claim 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 will not be able to market products or perform research and development or other activities covered by these patents.

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***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.***

A third party may sue us for infringing its 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 third-party proprietary rights. In addition, a third party may claim that we have improperly obtained or used its confidential or proprietary information. Furthermore, in connection with a license agreement, we have agreed to indemnify the licensor for costs incurred in connection with litigation relating to intellectual property rights. The cost to us of any litigation or other proceeding relating to intellectual property rights, even if resolved in our favor, could be substantial, and the litigation would divert our management s efforts. Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. Uncertainties resulting from the initiation and continuation of any litigation could limit our ability to continue our operations.

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

***If we fail to comply with our obligations under any licenses or related agreements, we could lose license rights that are necessary for developing and protecting our RNAi technology and any related product candidates that we develop, or we could lose certain exclusive rights to grant sublicenses.***

Our current licenses impose, and any future licenses we enter into are likely to impose, various development, commercialization, funding, royalty, diligence, sublicensing, insurance and other obligations on us. If we breach any of these obligations, the licensor may have the right to terminate the license or render the license non-exclusive, which could result in us being unable to develop, manufacture and sell products that are covered by the licensed technology or enable a competitor to gain access to the licensed technology. In addition, while we cannot currently determine the amount of the royalty obligations we will be required to pay on sales of future products, if any, the amounts may be significant. The amount of our future royalty obligations will depend on the technology and intellectual property we use in products that we successfully develop and commercialize, if any. Therefore, even if we successfully develop and commercialize products, we may be unable to achieve or maintain profitability.

For two important pending patent applications, owned in part or solely by the Max Planck organization of Germany, our amended licenses with Garching Innovation GmbH, a related entity to the Max Planck organization, require us to maintain a minimum level of employees in Germany. If we fail to comply with this condition, the owners of the patent applications that are the subject of these licenses may have the right to grant a similar license to one other company. We regard these pending patent applications as significant because they relate to important aspects of the structure of siRNA molecules and their use as therapeutics.

We have an agreement with Isis under which we were granted licenses to over 150 patents and patent applications that we believe will be useful to the development of RNAi therapeutics. If, by January 1, 2008, we or a collaborator have not completed the studies required for an investigational new drug application filing or similar foreign filing for at least one product candidate involving these patent rights, Isis would have the

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right to grant licenses to third parties for these patents and patent applications, thereby making our rights non-exclusive.

***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 Our Common Stock and this Offering

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

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

***We may incur significant costs from class action litigation due to our expected stock volatility.***

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

***If there are substantial sales of our common stock, the price of our common stock could decline.***

In connection with this offering, all of our executive officers and directors have entered into lock-up agreements with the underwriters for this offering. As a result of these lock-up agreements, approximately 0.6 million shares are subject to a contractual restriction on resale through the date that is 90 days after the date of this prospectus supplement or later if extended in accordance with the terms of the lock-up agreement. In addition, one other existing stockholder, which held approximately 1.4 million shares of our outstanding common stock as of January 15, 2006, has entered into a lock-up agreement with the underwriters for this offering providing for a 30-day restricted period. The market price for shares of our common stock may decline if stockholders subject to the lock-up agreements sell a substantial number of shares when the restrictions on resale lapse, or if the underwriters waive the lock-up agreements and allow the stockholders to sell some or all of their shares.

None of our other existing stockholders, including Abingworth BioVentures, ARCH Venture Fund, Atlas Venture and Polaris Venture Partners, which in the aggregate held approximately 5.4 million shares as of December 31, 2005, Merck and Isis, which in the aggregate held approximately 1.8 million shares as of December 31, 2005, and Novartis, which held approximately 5.3 million shares as of December 31, 2005, have entered into lock-up agreements with the underwriters for this offering. Substantially all of the shares of

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common stock held by such stockholders are freely tradable, tradable under Rule 144 or held by holders with demand registration rights. As of December 31, 2005, the holders of approximately 10.1 million shares of our common stock have rights to require us to file registration statements under the Securities Act of 1933, as amended, or the Securities Act, or to include their shares in registration statements that we may file in the future for ourselves or other stockholders. If our existing stockholders sell a large number of shares of our common stock or the public market perceives that existing stockholders might sell shares of common stock, the market price of our common stock could decline significantly.

***Insiders have substantial influence over Alnylam and could delay or prevent a change in corporate control.***

Our directors and executive officers, together with their affiliates, own, in the aggregate, approximately 15% of our outstanding common stock as of December 31, 2005. As a result, these stockholders, if acting together, may have the ability to significantly affect the outcome of matters submitted to our stockholders for approval, including the election of directors and any merger, consolidation or sale of all or substantially all of our assets. In addition, in October 2005, Novartis purchased 19.9% of our common stock outstanding as of the date of its purchase. Accordingly, these concentrations of ownership may harm the market price of our common stock by:

- delaying, deferring or preventing a change in control of our company;
- impeding a merger, consolidation, takeover or other business combination involving our company; or
- discouraging a potential acquirer from making a tender offer or otherwise attempting to obtain control of our company.

***Anti-takeover provisions in our charter documents and under Delaware law 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, in July 2005, our board of directors adopted a stockholder rights plan, the provisions of which could make it more difficult for a potential acquirer of Alnylam to consummate an acquisition transaction.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner. These provisions would apply even if the proposed merger or acquisition could be considered beneficial by some stockholders.

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

If you purchase common stock in this offering, you will incur an immediate and substantial dilution in net tangible book value of $9.87 per share, after giving effect to the sale by us of 5,115,961 shares of common stock offered in this offering at the price to public of $13.00 per share. 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 underwriters exercise their over-allotment option or Novartis Pharma AG exercises its right to purchase additional shares, you will incur additional dilution.

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

We intend to use the net proceeds from this offering for general corporate purposes, and therefore, our management will have broad discretion as to the use of the offering proceeds. Accordingly, you will 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 our company.

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## FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities 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 Securities Exchange Act. We use words such as anticipate, believe, estimate, expect, intend, may, plan, project, will, would and similar ex 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 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 undertake no 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.

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## USE OF PROCEEDS

We estimate that the net proceeds from the sale of the 5,115,961 shares of our common stock that we are offering at the price to public of $13.00 per share will be approximately $62.3 million, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us. We intend to use the net proceeds of this offering for general corporate purposes, including research and development expenses, clinical trial costs, general and administrative expenses and potential acquisitions of companies, products and technologies that complement our business. Pending the application of the net proceeds, we intend to invest the net proceeds in investment-grade, interest-bearing securities.

## PRICE RANGE OF OUR COMMON STOCK

Since May 28, 2004, our common stock has been quoted on the Nasdaq National Market under the trading symbol ALNY . The following table sets forth, for the period indicated, the high and low sale prices per share of the common stock as reported by the Nasdaq National Market.

| | Price Range of Common Stock | |
|---|---|---|
| | **High** | **Low** |
| **Year Ended December 31, 2004:** | | |
| Second Quarter (beginning May 28, 2004) | $ 9.50 | $ 5.26 |
| Third Quarter | $ 8.00 | $ 3.65 |
| Fourth Quarter | $ 8.60 | $ 5.00 |
| **Year Ended December 31, 2005:** | | |
| First Quarter | $ 11.00 | $ 6.76 |
| Second Quarter | $ 9.00 | $ 6.90 |
| Third Quarter | $ 15.22 | $ 6.90 |
| Fourth Quarter | $ 14.85 | $ 9.06 |
| **Year Ended December 31, 2006:** | | |
| First Quarter (through January 31, 2006) | $ 15.43 | $ 12.38 |

On January 31, 2006, the reported last sale price of our common stock on the Nasdaq National Market was $13.44 per share.

As of December 31, 2005, there were approximately 75 stockholders of record. This figure does not reflect persons or entities who hold their stock in nominee or street name through various brokerage firms.

## 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.

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## CAPITALIZATION

The following table sets forth our cash, cash equivalents and marketable securities and our capitalization as of September 30, 2005:

- on an actual basis; and
- on an as adjusted basis to give effect to the sale of 5,115,961 shares of common stock in this offering at the price to public of $13.00 per share, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

You should read this table in conjunction with Management s Discussion and Analysis of Financial Condition and Results of Operations and our financial statements and related footnotes incorporated by reference in the accompanying prospectus.

| | As of September 30, 2005 | |
|---|---|---|
| | Actual | As Adjusted |
| | ($ in thousands, except per share data) | |
| Cash, cash equivalents and marketable securities | $ 24,809 | $ 87,081 |
| Note payable, net of current portion | $ 5,782 | $ 5,782 |
| Stockholders equity: | | |
| Preferred stock, $0.01 par value, 5,000,000 shares authorized, no shares issued or outstanding | | |
| Common stock, $0.01 par value, 125,000,000 shares authorized, 21,286,058 shares issued and 21,203,164 shares outstanding, actual; and 26,402,019 shares issued and 26,319,125 shares outstanding, as adjusted | 212 | 263 |
| Additional paid-in capital | 117,176 | 179,397 |
| Deferred compensation | (2,857) | (2,857) |
| Accumulated other comprehensive loss | (32) | (32) |
| Accumulated deficit | (91,428) | (91,428) |
| Total stockholders equity | 23,071 | 85,343 |
| Total capitalization | $ 28,853 | $ 91,125 |

The actual amounts as of September 30, 2005 in the preceding table do not include the approximately $68.5 million of proceeds from the Novartis alliance that we received in October 2005. After giving effect to the receipt of a $10 million upfront payment and approximately $58.5 million related to the purchase by Novartis of 5,267,865 shares of our common stock, cash, cash equivalents and marketable securities would have been approximately $93.3 million, common stock would have been approximately $0.3 million, additional paid-in capital would have been approximately $169.3 million, total stockholders equity would have been approximately $75.2 million and total capitalization would have been approximately $81.0 million.

In the event that Novartis Pharma AG purchases all of the shares of common stock that it has the right to purchase from us in connection with this offering, each of the as adjusted cash, cash equivalents and marketable securities, as adjusted total stockholders equity and as adjusted total capitalization in the preceding table would increase by approximately $16.4 million, and if the option granted by us to the underwriters to purchase additional shares is exercised in full, by an additional approximately $2.5 million.

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## DILUTION

Our net tangible book value as of September 30, 2005 was approximately $20.0 million, or approximately $0.94 per share of common stock. Net tangible book value per share is calculated by subtracting our total liabilities from our total tangible assets, which is total assets less intangible assets, and dividing this amount by the number of shares of common stock outstanding. After giving effect to the sale by us of the 5,115,961 shares of common stock offered in this offering at the price to public of $13.00 per share and after deducting the underwriting discounts and commissions and estimated offering expenses payable by us, our net tangible book value as of September 30, 2005 would have been approximately $82.3 million, or approximately $3.13 per share of common stock. This represents an immediate increase in the net tangible book value of $2.18 per share to our existing stockholders and an immediate and substantial dilution in net tangible book value of $9.87 per share to new investors. The following table illustrates this per share dilution:

| | | |
|---|---|---|
| Price to public per share | | $ 13.00 |
| Net tangible book value per share as of September 30, 2005 | $ 0.94 | |
| Increase per share attributable to new investors | $ 2.18 | |
| Net tangible book value per share after this offering | | $ 3.13 |
| Dilution per share to new investors | | $ 9.87 |

In the discussion and table above, we assume no exercise of outstanding options or warrants. As of September 30, 2005, there were 3,180,472 shares of common stock reserved for issuance upon exercise of outstanding options with a weighted average exercise price of $3.58 per share and 52,630 shares of common stock reserved for issuance upon exercise of outstanding warrants with a weighted average exercise price of $9.50 per share. To the extent that any of these outstanding options and warrants are exercised, there will be further dilution to new investors. In addition, in the discussion and table above, we assume no exercise by the underwriters of their over-allotment option and no exercise by Novartis Pharma AG of its right to purchase shares in connection with this offering. If the underwriters exercise their over-allotment option or Novartis Pharma AG purchases additional shares, there will be further dilution to new investors.

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## UNDERWRITERS

Under the terms and subject to the conditions contained in an underwriting agreement dated the date of this prospectus supplement, the underwriters named below have severally agreed to purchase, and we have agreed to sell to them, severally, the number of shares indicated below.

| Name | Number of Shares |
|---|---|
| Morgan Stanley & Co. Incorporated | 2,557,982 |
| Banc of America Securities LLC | 1,125,511 |
| Piper Jaffray & Co. | 613,915 |
| SG Cowen & Co., LLC | 613,915 |
| Rodman & Renshaw, LLC | 204,638 |
| Total | 5,115,961 |

The underwriters are offering the shares of common stock subject to their acceptance of the shares from us and subject to prior sale. The underwriting agreement provides that the obligations of the several underwriters to pay for and accept delivery of the shares of common stock offered by this prospectus are subject to the approval of specified legal matters by their counsel and to other conditions. The underwriters are obligated to take and pay for all of the shares of common stock offered by this prospectus if any such shares are taken. However, the underwriters are not required to take or pay for the shares covered by the underwriters over-allotment option described below.

The underwriters initially propose to offer part of the shares of common stock directly to the public at the price to public listed on the cover page of this prospectus supplement and part to certain dealers at a price that represents a concession not in excess of $0.47 per share under the price to public. No underwriter may allow, and no dealer may re-allow, any concession to other underwriters or to certain dealers. After the initial offering of the shares of common stock, the offering price and other selling terms may from time to time be varied by the representatives.

We have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus supplement, to purchase up to an aggregate of 767,394 additional shares of common stock at the price to public listed on the cover page of this prospectus supplement, less underwriting discounts and commissions. The underwriters may exercise this option solely for the purpose of covering over-allotments, if any, made in connection with the offering of the shares of common stock offered by this prospectus. To the extent the option is exercised, each underwriter will become obligated, subject to certain conditions, to purchase approximately the same percentage of the additional shares of common stock as the number listed next to the underwriter s name in the preceding table bears to the total number of shares of common stock listed next to the names of all underwriters in the preceding table. If the underwriters option is exercised in full, the total price to public would be $76,483,615, the total underwriters discounts and commissions would be $4,589,017 and the total proceeds to us would be $71,894,598.

We and each of our directors and executive officers have agreed that, without the prior written consent of Morgan Stanley & Co. Incorporated on behalf of the underwriters, we and they will not, during the period ending 90 days after the date of this prospectus supplement:

- 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, lend or otherwise transfer or dispose of, directly or indirectly, any shares of our common stock or any securities convertible into or exercisable or exchangeable for shares of our common stock; or

- enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of shares of our common stock,

whether any transaction described above is to be settled by delivery of shares of our common stock or such other securities, in cash or otherwise.

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In addition, we have agreed not to, without the prior written consent of Morgan Stanley & Co. Incorporated on behalf of the underwriters, during the period ending 90 days after the date of this prospectus supplement, file a registration statement, other than a registration statement on Form S-8 and a registration statement relating to the resale of up to 500,000 shares of common stock issued by us in connection with a strategic alliance, license, acquisition agreement or loan agreement, with the Securities and Exchange Commission relating to an offering by us of any shares of our common stock or securities convertible into or exercisable or exchangeable for common stock. Each of our directors and executive officers has also agreed not to, without the prior written consent of Morgan Stanley & Co. Incorporated on behalf of the underwriters, during the period ending 90 days after the date of this prospectus supplement, make any demand for or exercise any rights relating to the registration of any shares of our common stock or any securities convertible into or exercisable or exchangeable for our common stock.

Subject to certain limitations, the restrictions applicable to our directors and executive officers do not apply to:

- transactions relating to shares of our common stock or other securities acquired in open market transactions after the completion of this offering, provided that no filing under Section 16(a) of the Securities Exchange Act of 1934, as amended, shall be required or voluntarily made in connection with subsequent sales of such common stock or other securities;

- transfers of shares of common stock or any security convertible into or exercisable for common stock as a bona fide gift or by will or intestate succession, or distributions to limited partners, members or stockholders of the transferor; provided that the transferee, donee or distributee agrees to be bound by such restrictions;

- the exercise of an option to purchase shares of common stock granted under our stock incentive or purchase plan, provided that the shares issued upon such exercise shall be subject to the restrictions described above; or

- transactions relating to common stock acquired in this offering.

Subject to certain limitations, the restrictions applicable to us do not apply to:

- the sale of shares of our common stock to the underwriters;

- the issuance by us of shares under our employee stock purchase plan or upon the exercise of outstanding options, warrants or other securities;

- the grant of options to purchase shares of our common stock, provided that such options do not vest during the restricted period;

- the issuance of shares to Novartis pursuant to our investor rights agreement with Novartis or to Medtronic pursuant to our collaboration agreement with Medtronic; or

- the issuance of up to 4,000,000 shares pursuant to strategic alliances, licenses, acquisition agreements or loan agreements that we may enter into after the date of this prospectus supplement, provided that, with the exception of up to 500,000 of such shares, such shares shall be subject to the restrictions described above.

The 90-day restricted period described above is subject to extension such that, in the event that either (1) during the last 17 days of the 90-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 90-day restricted period, we announce that we will release earnings results during the 16-day period beginning on the last day of the 90-day period and in each of case (1) and (2), if, at the end of the 90-day restricted period, (i) our shares are not actively traded securities as such term is defined in Regulation M under the Securities Act, or (ii) the underwriters are not able to publish or distribute research reports concerning Alnylam or its industry pursuant to Rule 139 of the Securities Act, the lock-up restrictions described above, subject to limited exceptions, will 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.

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In addition, a holder of approximately 1.4 million shares of our common stock as of January 15, 2006 has agreed to the restrictions on transfer described above applicable to our directors and executive officers, except that the restricted period for such stockholder is 30 days after the date of this prospectus supplement.

Our common stock is quoted on the Nasdaq National Market under the trading symbol ALNY .

The following table shows the underwriting discounts and commissions that we are to pay to the underwriters in connection with this offering. These amounts are shown assuming both no exercise and full exercise of the underwriters option to purchase additional shares of our common stock.

| | Paid by Alnylam Pharmaceuticals, Inc. | |
|---|---|---|
| | No Exercise | Full Exercise |
| Per share | $ 0.78 | $ 0.78 |
| Total | $ 3,990,450 | $ 4,589,017 |

In addition, we estimate that the expenses of this offering payable by us, other than underwriting discounts and commissions, will be $245,000.

In order to facilitate the offering of our common stock, the underwriters may engage in transactions that stabilize, maintain or otherwise affect the price of our common stock. Specifically, the underwriters may sell more shares than they are obligated to purchase under the underwriting agreement, creating a short position. A short sale is covered if the short position is no greater than the number of shares available for purchase by the underwriters under the over-allotment option. The underwriters can close out a covered short sale by exercising the over-allotment option or purchasing shares in the open market. In determining the source of shares to close out a covered short sale, the underwriters will consider, among other things, the open market price of shares compared to the price available under the over-allotment option. The underwriters may also sell shares in excess of the over-allotment option, creating a naked short position. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of our common stock in the open market after pricing that could adversely affect investors who purchase in this offering. In addition, to stabilize the price of our common stock, the underwriters may bid for, and purchase, shares of our common stock in the open market. Finally, the underwriting syndicate may reclaim selling concessions allowed to an underwriter or a dealer for distributing our common stock in this offering, if the syndicate repurchases previously distributed common stock in transactions to cover syndicate short positions or to stabilize the price of our common stock. Any of these activities may stabilize or maintain the market price of our common stock above independent market levels. The underwriters are not required to engage in these activities, and may end any of these activities at any time.

In general, purchases of a security for the purpose of stabilizing or reducing a syndicate short position could cause the price of the security to be higher than it might otherwise be in the absence of such purchases.

Neither we nor the underwriters make any representation or prediction as to the direction or magnitude of any effect that the transactions described above may have on the price of the common stock.

In addition, neither we nor the underwriters make any representation that the underwriters will engage in such transactions or that such transactions will not be discontinued without notice, once they are commenced. In connection with this offering, either of the underwriters and any selling group members who are a qualified market maker on the Nasdaq National Market, may engage in passive market making transactions in the common stock on the Nasdaq National Market in accordance with Rule 103 of Regulation M under the Securities Exchange of 1934, as amended, during the business day before the pricing of this offering, before the commencement of offers or sales of the common stock. Passive market makers must comply with applicable volume and price limitations and must be identified as passive market makers. In general, a passive market maker must display its bid at a price not in excess of the highest independent bid for the security; if all independent bids are lowered below the passive market maker s bid, however

the bid must then be lowered when purchase limits are exceeded.

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We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act. If we are unable to provide this indemnification, we will contribute to payments the underwriters may be required to make in respect of those liabilities.

The underwriters and their affiliates have provided and may provide financial advisory and investment banking services to certain former and existing stockholders and us, for which they receive customary fees.

In compliance with NASD guidelines, the maximum compensation to the underwriters in connection with the sale of the shares of common stock pursuant to this prospectus supplement and the accompanying prospectus will not exceed 8% of the total public offering price to the public of the shares of common stock as set forth on the cover page of this prospectus supplement.

The price to public has been determined by negotiations between us and the representatives. Among the factors considered in determining the price to public were the current market price of our common stock, our future prospects and those of our industry in general, sales, earnings and certain other financial operating information of our company in recent periods, and the price-earnings ratios, price-sale ratios, market prices of securities and certain financial and operating information of companies engaged in activities similar to ours.

**European Economic Area**

In relation to each Member State of the European Economic Area which has implemented the Prospectus Directive, each underwriter has represented and agreed that with effect from and including the date on which the Prospectus Directive is implemented in that Member State it has not made and will not make an offer of shares to the public in that Member State, except that it may, with effect from and including such date, make an offer of shares to the public in that Member State:

(a) at any time to legal entities which are authorised or regulated to operate in the financial markets or, if not so authorised or regulated, whose corporate purpose is solely to invest in securities;

(b) at any time to any legal entity which has two or more of (1) an average of at least 250 employees during the last financial year; (2) a total balance sheet of more than 43,000,000 and (3) an annual net turnover of more than 50,000,000, as shown in its last annual or consolidated accounts; or

(c) at any time in any other circumstances which do not require the publication by us of a prospectus pursuant to Article 3 of the Prospectus Directive.

For the purposes of the above, the expression an offer of shares to the public in relation to any shares in any Member State means the communication in any form and by any means of sufficient information on the terms of the offer and the shares to be offered so as to enable an investor to decide to purchase or subscribe the shares, as the same may be varied in that Member State by any measure implementing the Prospectus Directive in that Member State and the expression Prospectus Directive means Directive 2003/71/EC and includes any relevant implementing measure in that Member State.

**United Kingdom**

Each underwriter has represented and agreed that 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 2000) in connection with the issue or sale of the shares in circumstances in which Section 21(1) of such Act does not apply to us and it has complied and will comply with all applicable provisions of such Act with respect to anything done by it in relation to any shares in, from or otherwise involving the United Kingdom.

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## LEGAL MATTERS

The validity of the common stock offered will be passed upon for us by Wilmer Cutler Pickering Hale and Dorr LLP, Boston, Massachusetts. Steven D. Singer, a partner in the law firm of Wilmer Cutler Pickering Hale and Dorr LLP, is our Secretary. Shearman & Sterling LLP will pass upon certain legal matters in connection with this offering for the underwriters.

## EXPERTS

The financial statements incorporated in this prospectus supplement by reference to the Annual Report on Form 10-K for the year ended December 31, 2004 have been so incorporated in reliance on the reports of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in auditing and accounting.

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**PROSPECTUS**

**$75,000,000**

# ALNYLAM PHARMACEUTICALS, INC.

**Common Stock**

We may from time to time sell common stock in one or more offerings for an aggregate initial offering price of $75,000,000. This prospectus describes the general manner in which our common stock may be offered using this prospectus. We will specify in the accompanying prospectus supplement the terms of the securities to be offered and sold. We may sell these securities to or through underwriters or dealers and also to other purchasers or through agents. We will set forth the names of any underwriters, dealers or agents in the accompanying prospectus supplement.

Our common stock is quoted on the Nasdaq National Market under the trading symbol ALNY . The reported last sale price of our common stock on the Nasdaq National Market on December 15, 2005 was $12.90 per share.

**Investing in our common stock involves risks. See Risk Factors on page 1 of this prospectus.**

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.

This prospectus may not be used to consummate sales of securities unless it is accompanied by a prospectus supplement.

**Prospectus dated December 20, 2005.**

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**You should rely only on the information contained in this prospectus and the documents incorporated by reference in this prospectus or to which we have referred you. We have not, and the underwriters have not, authorized anyone to provide you with different information. If anyone provides you with different or inconsistent information, you should not rely on it. This prospectus does not constitute an offer to sell, or a solicitation of an offer to purchase, the securities offered by this 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. You should not assume that the information contained in this prospectus or any document incorporated by reference is accurate as of any date other than the date on the front cover of the applicable document. Neither the delivery of this prospectus nor any distribution of securities pursuant to this prospectus shall, under any circumstances, create any implication that there has been no change in the information set forth or incorporated by reference into this prospectus or in our affairs since the date of this prospectus. Our business, financial condition, results of operations and prospects may have changed since that date.**

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## ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission using a shelf registration process. Under this shelf registration process, we may, from time to time, sell common stock in one or more offerings up to a total dollar amount of $75,000,000. This prospectus describes the general manner in which our common stock may be offered by this prospectus. Each time we sell common stock, we will provide a prospectus supplement that will contain specific information about the terms of that offering. If there is any inconsistency between the information in this prospectus and the accompanying prospectus supplement, you should rely on the information in the prospectus supplement. We may also add, update or change in the prospectus supplement any of the information contained in this prospectus. This prospectus, together with applicable prospectus supplements, includes all material information relating to this offering.

## ALNYLAM PHARMACEUTICALS, INC.

Alnylam Pharmaceuticals, Inc. is a biopharmaceutical company seeking to develop and commercialize new drugs that work through a recently discovered system in cells known as RNA interference, or RNAi. RNAi is a natural mechanism for selectively silencing genes. Genes provide cells with coded instructions for making proteins, and silencing a gene refers to stopping or reducing production of the protein specified, or encoded, by that gene. Using our intellectual property and the expertise we have built in RNAi, we are developing a set of biological and chemical methods and know-how that we expect to apply in a systematic way to develop RNAi therapeutics for a variety of diseases. We have initiated programs to develop RNAi therapeutics that will be administered directly to diseased parts of the body, which we refer to as Direct RNAi™ therapeutics. We currently have two development programs and a number of preclinical programs for Direct RNAi therapeutics. The development programs are focused on respiratory infections caused by human respiratory syncytial virus, or RSV, and influenza. In pre-clinical programs, we are also working on the inherited respiratory disease known as cystic fibrosis. We have additional pre-clinical programs in Direct RNAi focused on a central nervous system disorder known as Parkinson s disease and in spinal cord injury and neuropathic pain. We are also working to extend our capabilities to enable the development of RNAi therapeutics that travel through the bloodstream to reach diseased parts of the body, which we refer to as Systemic RNAi™.

We were incorporated in Delaware in May 2003 as Alnylam Holding Co. In February 2004, we changed our name to Alnylam Pharmaceuticals, Inc. Alnylam Europe AG, which was incorporated in Germany in June 2000 under the name Ribopharma AG, and Alnylam U.S., Inc., which was incorporated in Delaware in June 2002, are wholly-owned subsidiaries of Alnylam Pharmaceuticals, Inc. We acquired Alnylam Europe AG in July 2003. 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 is www.alnylam.com. The information on our website is not incorporated by reference into this prospectus or any prospectus supplement and should not be considered to be a part of this prospectus or any prospectus supplement. We have included our website address as an inactive textual reference only.

Unless otherwise stated, all references to us, our, Alnylam, we, the Company and similar designations refer t Alnylam Pharmaceuticals, Inc. and our subsidiaries. Our logo, trademarks and service marks are the property of Alnylam. Other trademarks or service marks appearing in this prospectus, any prospectus supplement or any document incorporated by reference in this prospectus are the property of their respective holders.

## RISK FACTORS

An investment in our common stock involves significant risks. You should carefully consider the risk factors contained in any prospectus supplement and in our filings with the Securities and Exchange Commission, as well as all of information contained in this prospectus, any prospectus supplement and the documents incorporated by reference in this prospectus, before you decide to invest in our common stock.

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The risks and uncertainties we have described are not the only ones we face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our operations.

## SPECIAL NOTE REGARDING FORWARD-LOOKING INFORMATION

This prospectus, any prospectus supplement and the documents we incorporate by reference in this prospectus contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, or the Exchange Act. All statements, other than statements of historical facts, that we include in this prospectus, any prospectus supplement and in the documents we incorporate by reference in this prospectus, may be deemed forward-looking statements for purposes of the Securities Act and the Exchange Act. We use the words anticipate, believe, estimate, expect, intend, may, plan, pro would and similar expressions to identify forward-looking statements, although not all forward-looking statements contain these identifying words. 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 the forward-looking statements that we make, including the factors included in the documents we incorporate by reference in this prospectus. You should read these factors and the other cautionary statements made in the documents we incorporate by reference as being applicable to all related forward-looking statements wherever they appear in this prospectus, any prospectus supplement and any document incorporated by reference. We caution you that we do not undertake any obligation to update forward-looking statements we make.

## USE OF PROCEEDS

Unless otherwise provided in the applicable prospectus supplement, we intend to use the net proceeds from the sale of our common stock under this prospectus for general corporate purposes, including research and development expenses, clinical trial costs, general and administrative expenses and potential acquisitions of companies, products and technologies that complement our business. We will set forth in the prospectus supplement our intended use for the net proceeds received from the sale of our common stock. Pending the application of the net proceeds, we intend to invest the net proceeds in investment-grade, interest-bearing securities.

## PLAN OF DISTRIBUTION

We may sell our common stock through underwriters or dealers, through agents, or directly to one or more purchasers. The accompanying prospectus supplement will describe the terms of the offering of our common stock, including:

- the number of shares of common stock we are offering;
- the name or names of any underwriters;
- any securities exchange or market on which the common stock may be listed;
- the purchase price of our common stock being offered and the proceeds we will receive from the sale;
- any over-allotment options pursuant to which underwriters may purchase additional shares of common stock from us;

any underwriting discounts or agency fees and other items constituting underwriters or agents compensation; and

any discounts or concessions allowed or reallowed or paid to dealers.

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If underwriters are used in the sale, they will acquire the common stock for their own account and may resell the common stock from time to time in one or more transactions at a fixed public offering price or at varying prices determined at the time of the sale. The obligations of the underwriters to purchase the common stock will be subject to the conditions set forth in the applicable underwriting agreement. We may offer the common stock to the public through underwriting syndicates represented by managing underwriters or by underwriters without a syndicate. Subject to certain conditions, the underwriters will be obligated to purchase all the shares of common stock offered by the prospectus supplement. We may change from time to time the public offering price and any discounts or concessions allowed or reallowed or paid to dealers.

We may sell our common stock directly or through agents we designate from time to time. We will name any agent involved in the offering and sale of our common stock, and we will describe any commissions we will pay the agent in the prospectus supplement. Unless the prospectus supplement states otherwise, our agent will act on a best-efforts basis for the period of its appointment.

We may provide underwriters and agents with indemnification against civil liabilities related to this offering, including liabilities under the Securities Act, or contribution with respect to payments that the underwriters or agents may make with respect to these liabilities. Underwriters and agents may engage in transactions with, or perform services for, us in the ordinary course of business. We will describe such relationships in the prospectus supplement naming the underwriter and the nature of any such relationship.

Rules of the Securities and Exchange Commission may limit the ability of any underwriters to bid for or purchase shares of common stock before the distribution of the shares of common stock is completed. However, underwriters may engage in the following activities in accordance with the rules:

*Stabilizing transactions* Underwriters may make bids or purchases for the purpose of pegging, fixing or maintaining the price of the shares, so long as stabilizing bids do not exceed a specified maximum.

*Over-allotments and syndicate covering transactions* Underwriters may sell more shares of our common stock than the number of shares that they have committed to purchase in any underwritten offering. This over-allotment creates a short position for the underwriters. This short position may involve either covered short sales or naked short sales. Covered short sales are short sales made in an amount not greater than the underwriters over-allotment option to purchase additional shares in any underwritten offering. The underwriters may close out any covered short position either by exercising their over-allotment option or by purchasing shares in the open market. To determine how they will close the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market, as compared to the price at which they may purchase shares through the over-allotment option. Naked short sales are short sales in excess of the over-allotment option. The underwriters must close out any naked position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that, in the open market after pricing, there may be downward pressure on the price of the shares that could adversely affect investors who purchase shares in the offering.

*Penalty bids* If underwriters purchase shares in the open market in a stabilizing transaction or syndicate covering transaction, they may reclaim a selling concession from other underwriters and selling group members who sold those shares as part of the offering.

Similar to other purchase transactions, an underwriter s purchases to cover the syndicate short sales or to stabilize the market price of our common stock may have the effect of raising or maintaining the market price of our common stock or preventing or mitigating a decline in the market price of our common stock. As a result, the price of the shares of our common stock may be higher than the price that might otherwise exist in the open market. The imposition of a penalty bid might also have an effect on the price of shares if it discourages resales of the shares.

If commenced, the underwriters may discontinue any of these activities at any time.

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Our common stock is quoted on the Nasdaq National Market. One or more underwriters may make a market in our common stock, but the underwriters will not be obligated to do so and may discontinue market making at any time without notice. We cannot give any assurance as to liquidity of the trading market for our common stock.

Any underwriters who are qualified market makers on the Nasdaq National Market may engage in passive market making transactions in the common stock on the Nasdaq National Market in accordance with Rule 103 of Regulation M, during the business day prior to the pricing of the offering, before the commencement of offers or sales of the common stock. Passive market makers must comply with applicable volume and price limitations and must be identified as passive market makers. In general, a passive market maker must display its bid at a price not in excess of the highest independent bid for such security; if all independent bids are lowered below the passive market maker s bid, however, the passive market maker s bid must then be lowered when certain purchase limits are exceeded.

In compliance with guidelines of the National Association of Securities Dealers, or NASD, the maximum consideration or discount to be received by any NASD member or independent broker dealer may not exceed 8% of the aggregate amount of the securities offered pursuant to this prospectus and any applicable prospectus supplement.

## LEGAL MATTERS

The validity of the common stock offered will be passed upon for us by Wilmer Cutler Pickering Hale and Dorr LLP, Boston, Massachusetts.

## EXPERTS

The financial statements incorporated in this prospectus by reference to the Annual Report on Form 10-K for the year ended December 31, 2004 have been so incorporated in reliance on the reports of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in auditing and accounting.

## WHERE YOU CAN FIND MORE INFORMATION

We file reports, proxy statements and other documents with the Securities and Exchange Commission. You may read and copy any document we file with the SEC at the SEC s Public Reference Room at 100 F Street, N.E., Room 1580, Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information on the public reference room.

The SEC also maintains an Internet site, the address of which is *www.sec.gov.* That site also contains our annual, quarterly and current reports, proxy statements, information statements and other information.

We have filed this prospectus with the SEC as part of a registration statement on Form S-3 under the Securities Act. This prospectus does not contain all of the information set forth in the registration statement because some parts of the registration statement are omitted in accordance with the rules and regulations of the SEC. You can obtain a copy of the registration statement from the SEC at the address listed above or from the SEC s Internet site.

We also maintain an Internet site at *www.alnylam.com,* through which you can access our SEC filings. The information set forth on our Internet site is not part of this prospectus.

## INCORPORATION OF DOCUMENTS BY REFERENCE

We are incorporating by reference certain documents we file with the SEC, which means that we can disclose important information to you by referring you to those documents. The information in the

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documents incorporated by reference is considered to be part of this prospectus. Statements contained in documents that we file with the SEC and that are incorporated by reference in this prospectus will automatically update and supersede information contained in this prospectus, including information in previously filed documents or reports that have been incorporated by reference in this prospectus, to the extent the new information differs from or is inconsistent with the old information.

We have filed or may file the following documents with the SEC. These documents are incorporated herein by reference as of their respective dates of filing:

Our Annual Report on Form 10-K for the fiscal year ended December 31, 2004, as filed with the SEC on March 30, 2005;

Our Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2005, as filed with the SEC on May 16, 2005;

Our Quarterly Report on Form 10-Q for the quarterly period ended June 30, 2005, as filed with the SEC on August 11, 2005;

Our Quarterly Report on Form 10-Q for the quarterly period ended September 30, 2005, as filed with the SEC on November 14, 2005;

Our Current Report on Form 8-K, as filed with the SEC on January 3, 2005;

Our Current Report on Form 8-K, as filed with the SEC on February 10, 2005;

Our Current Report on Form 8-K, as filed with the SEC on May 17, 2005;

Our Current Report on Form 8-K, as filed with the SEC on June 10, 2005;

Our Current Report on Form 8-K, as filed with the SEC on June 16, 2005;

Our Current Report on Form 8-K, as filed with the SEC on June 24, 2005;

Our Current Report on Form 8-K, as filed with the SEC on July 13, 2005;

Our Current Report on Form 8-K, as filed with the SEC on July 14, 2005;

Our Current Report on Form 8-K, as filed with the SEC on September 12, 2005;

Our Current Report on Form 8-K, as filed with the SEC on September 26, 2005;

Our Current Report on Form 8-K, as filed with the SEC on October 12, 2005;

Our Current Report on Form 8-K, as filed with the SEC on December 13, 2005;

All documents filed by us pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act (1) after the date of the filing of this registration statement and prior to its effectiveness and (2) until all of the common stock to which this prospectus relates has been sold or the offering is otherwise terminated, 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, will be deemed to be incorporated by reference in this prospectus and the accompanying prospectus supplement and to be a part hereof from the date of filing of such documents; 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.

You may request, orally or in writing, a copy of any of these documents, which will be provided to you at no cost, by contacting Cynthia Clayton, Director, Investor Relations and Corporate Communications, Alnylam Pharmaceuticals, Inc., 300 Third Street, Cambridge, MA 02142, telephone (617) 551-8200.

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