

ALNYLAM PHARMACEUTICALS, INC.

Form S-3

July 21, 2011

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As filed with the Securities and Exchange Commission on July 21, 2011

Registration No. 333-

UNITED STATES SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549
Form S-3

REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933
ALNYLAM PHARMACEUTICALS, INC.
(Exact name of registrant as specified in its charter)

Delaware
*(State or other jurisdiction of
incorporation or organization)*

77-0602661
*(I.R.S. Employer
Identification Number)*

300 Third Street
Cambridge, Massachusetts 02142
(617) 551-8200

*(Address, Including Zip Code, and Telephone Number, Including Area Code, of Registrant's Principal Executive
Offices)*

John M. Maraganore, Ph.D.
Chief Executive Officer
Alnylam Pharmaceuticals, Inc.
300 Third Street
Cambridge, Massachusetts 02142
(617) 551-8200

(Name, Address, Including Zip Code, and Telephone Number, Including Area Code, of Agent for Service)

Copy to:

Lia Der Marderosian, Esq.
Wilmer Cutler Pickering Hale and Dorr LLP
60 State Street
Boston, Massachusetts 02109
Telephone: (617) 526-6000
Telecopy: (617) 526-5000

Approximate date of commencement of proposed sale to the public: From time to time after this registration statement becomes effective.

If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box.

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box.

If this Form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box.

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

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

CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities to be Registered(1)	Proposed Maximum Aggregate Offering Price(1)	Amount of Registration Fee(1)
Debt Securities		
Common Stock, par value \$0.01 per share(2)		
Preferred Stock, par value \$0.01 per share		
Purchase Contracts		
Purchase Units(3)		
Warrants		
Total	\$150,000,000	\$17,415

(1) An indeterminate amount of the securities of each identified class is being registered as may from time to time be offered hereunder at indeterminate prices, along with an indeterminate number of securities that may be issued

upon exercise, settlement, exchange or conversion of securities offered or sold hereunder. Separate consideration may or may not be received for securities that are issuable upon conversion, exercise or exchange of other securities. In addition, the total amount to be registered and the proposed maximum aggregate offering price are estimated solely for the purpose of calculating the registration fee pursuant to Rule 457(o) under the Securities Act of 1933, as amended (the Securities Act).

- (2) Each share of common stock includes one Series A Right, which represents the right to purchase 1/1000th of a share of Series A Junior Participating Preferred Stock, par value \$0.01 per share. The value attributable to the Series A Right, if any, will be reflected in the offering price of the common stock.
- (3) Consisting of some or all of the securities listed above, in any combination, including common stock, preferred stock, debt securities and warrants.

The Registrant hereby amends this Registration Statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment which specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act or until the Registration Statement shall become effective on such date as the Commission acting pursuant to said Section 8(a), may determine.

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The information in this prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities and we are not soliciting offers to buy these securities in any jurisdiction where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED July 21, 2011

PROSPECTUS

\$150,000,000

**Debt Securities
Common Stock
Preferred Stock
Purchase Contracts
Purchase Units
Warrants**

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

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

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

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

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

The date of this prospectus is _____, 2011

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ABOUT THIS PROSPECTUS

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

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

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

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

WHERE YOU CAN FIND MORE INFORMATION

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

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

INCORPORATION BY REFERENCE

The SEC allows us to incorporate by reference much of the information we file with the SEC, which means that we can disclose important information to you by referring you to those publicly available documents. The information

that we incorporate by reference in this prospectus is considered to be part of this prospectus. Because we are incorporating by reference future filings with the SEC, this prospectus is continually updated and those future filings may modify or supersede some of the information included or

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

Annual Report on Form 10-K for the fiscal year ended December 31, 2010, including the information specifically incorporated by reference into the Annual Report on Form 10-K from our definitive proxy statement for the 2011 Annual Meeting of Stockholders;

Quarterly Report on Form 10-Q for the fiscal quarter ended March 31, 2011;

Current Reports on Form 8-K filed on February 7, 2011, March 3, 2011, March 15, 2011, March 17, 2011, March 23, 2011, March 25, 2011, April 7, 2011, May 2, 2011, June 7, 2011, June 10, 2011, June 13, 2011 and June 29, 2011; and

The description of our common stock and rights plan contained in Amendment No. 2 to our Registration Statement to Form 8-A on Form 8-A/A filed on July 14, 2005, including any amendments or reports filed for the purpose of updating such description.

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

**Alnylam Pharmaceuticals, Inc.
300 Third Street
Cambridge, Massachusetts 02142
Attn: Investor Relations
(617) 551-8200**

FORWARD-LOOKING STATEMENTS

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

ABOUT ALNYLAM PHARMACEUTICALS, INC.

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

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have built in RNAi, we are developing a set of biological and chemical methods and know-how that we apply in a systematic way to develop RNAi therapeutics for a variety of diseases.

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

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

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

CONSOLIDATED RATIOS OF EARNINGS TO FIXED CHARGES

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

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

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

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

\$42,098,000, \$16,240,000, \$79,146,000 and \$34,608,000, respectively, to achieve a coverage ratio of 1:1 in those periods.

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

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USE OF PROCEEDS

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

DILUTION

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

the net tangible book value per share of our equity securities before and after the offering;

the amount of the increase in such net tangible book value per share attributable to the cash payments made by the purchasers in the offering; and

the amount of the immediate dilution from the public offering price which will be absorbed by such purchasers.

DESCRIPTION OF CAPITAL STOCK

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

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

Common Stock

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

stockholders entitled to vote thereon at a duly held meeting of stockholders at which a quorum is present.

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

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

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

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

convert the stock into any other security;

have the stock redeemed; or

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

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

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

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

Preferred Stock

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

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

Our board of directors has authorized the issuance of Series A junior participating preferred stock, see Series A Junior Participating Preferred Stock, which includes terms and conditions that could discourage a takeover or other transaction that holders of some or a majority of our common stock might believe to be in their best interests. Any other series of our preferred stock could also, depending on the terms of such series, impede the completion of a merger, tender offer or other takeover attempt. Our board of directors will make

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any determination to issue such shares based upon its judgment as to the best interests of our stockholders. Our directors, in so acting, could issue preferred stock having terms that could discourage an acquisition attempt through which an acquirer may be able to change the composition of our board of directors, including a tender offer or other transaction that some, or a majority, of our stockholders might believe to be in their best interests or in which stockholders might receive a premium for their stock over the then-current market price of the stock.

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

the designation and stated value per share of the preferred stock and the number of shares offered;

the amount of liquidation preference per share;

the price at which the preferred stock will be issued;

the dividend rate, or method of calculation of dividends, the dates on which dividends will be payable, whether dividends will be cumulative or noncumulative and, if cumulative, the dates from which dividends will commence to accumulate;

any redemption or sinking fund provisions;

if other than the currency of the United States, the currency or currencies including composite currencies in which the preferred stock is denominated and/or in which payments will or may be payable;

any conversion provisions; and

any other rights, preferences, privileges, limitations and restrictions on the preferred stock.

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

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

senior to our common stock and to all equity securities ranking junior to such preferred stock with respect to dividend rights or rights upon our liquidation, dissolution or winding up of our affairs;

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

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

The term "equity securities" does not include convertible debt securities.

Dividends. Holders of the preferred stock of each series will be entitled to receive, when, as and if declared by our board of directors, cash dividends at such rates and on such dates described in the applicable prospectus supplement. Different series of preferred stock may be entitled to dividends at different rates or based on different methods of calculation. The dividend rate may be fixed or variable or both. Dividends will be payable to the holders of record as they appear on our stock books on record dates fixed by our board of directors, as specified in the applicable prospectus supplement.

Dividends on any series of preferred stock may be cumulative or noncumulative, as described in the applicable prospectus supplement. If our board of directors does not declare a dividend payable on a dividend

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

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

No dividends may be declared or paid or funds set apart for the payment of dividends on any junior securities unless full dividends for all dividend periods terminating on or prior to the date of the declaration or payment will have been paid or declared and a sum sufficient for the payment set apart for payment on the preferred stock.

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

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

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

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

or to the extent the net proceeds from any issuance are insufficient to pay in full the aggregate redemption price then due, such preferred stock shall automatically and mandatorily be converted into the applicable shares of our capital stock pursuant to conversion provisions

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specified in the applicable prospectus supplement. Notwithstanding the foregoing, we will not redeem any preferred stock of a series unless:

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

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

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

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

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

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

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

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

the redemption date;

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

the redemption price;

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

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

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

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

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

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

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

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

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

Series A Junior Participating Preferred Stock

In July 2005, our board of directors declared a dividend of one right, collectively, the Rights, to buy one one-thousandth of a share of newly designated Series A junior participating preferred stock for each outstanding share of our common stock to stockholders of record at the close of business on July 26, 2005. Initially, the Rights are not exercisable and will be attached to all certificates representing outstanding shares of common stock. The Rights will expire at the close of business on July 13, 2015 unless earlier redeemed or exchanged. Until a Right is exercised, the holder thereof will have no rights as a stockholder of Alnylam, including the right to vote or to receive dividends. Subject to the terms and conditions of the rights agreement, the Rights will become exercisable upon the earlier of (1) ten business days following the later of (a) the first date of a public announcement that a person or group, referred to as an Acquiring Person, acquires, or obtained the right to acquire, beneficial ownership of 20% or more of the outstanding shares of our common stock or (b) the first date on which an executive officer of Alnylam has actual knowledge that an Acquiring Person has become such or (2) ten business days following the commencement of a tender offer or exchange offer that would result in a person or group beneficially owning more than 20% of the outstanding shares of our common stock. Each Right entitles the holder to purchase one one-thousandth of a share of Series A junior preferred stock at an initial purchase price of \$80.00 in cash, subject to adjustment. In the event that any person or group becomes an Acquiring Person, subject to certain exceptions, each Right not owned by the Acquiring Person will entitle its holder to receive, upon exercise, that number of shares of our common stock (or in certain circumstances, cash, property or other securities) which equals the exercise price of the Right divided by 50% of the current market price (as defined in the Rights Agreement) per share of such common stock at the date of the occurrence of the event.

Effects of Authorized but Unissued Stock

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

could adversely affect the voting power of holders of common stock and the likelihood that such holders will receive dividend payments and payments upon liquidation.

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

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

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

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

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

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

a merger with, disposition of significant assets to or receipt of disproportionate financial benefits by the interested stockholder, and

any other transaction that would increase the interested stockholder's proportionate ownership of any class or series of our capital stock.

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

The prohibition against these transactions does not apply if:

prior to the time that any stockholder became an interested stockholder, the board of directors approved either the business combination or the transaction in which such stockholder acquired 15% or more of our outstanding voting stock, or

the interested stockholder owns at least 85% of our outstanding voting stock as a result of a transaction in which such stockholder acquired 15% or more of our outstanding voting stock. Shares held by persons who are both directors and officers or by some types of employee stock plans are not counted as outstanding when making this calculation.

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Directors Liability

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

for any breach of the director's legal duty to act in the best interests of us and our stockholders;

for acts or omissions by the director with dishonest intentions or which involve intentional misconduct or an intentional violation of the law;

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

for transactions where the director derived an improper personal benefit.

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

DESCRIPTION OF DEBT SECURITIES

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

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

General

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

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

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

the debt securities designation;

the aggregate principal amount of the debt securities;

the percentage of their principal amount (i.e., price) at which the debt securities will be issued;

the date or dates on which the debt securities will mature and the right, if any, to extend such date or dates;

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the rate or rates, if any, per year, at which the debt securities will bear interest, or the method of determining such rate or rates;

the date or dates from which such interest will accrue, the interest payment dates on which such interest will be payable or the manner of determination of such interest payment dates and the record dates for the determination of holders to whom interest is payable on any interest payment date;

the right, if any, to extend the interest payment periods and the duration of that extension;

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

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

the period or periods, if any, within which, the price or prices at which, and the terms and conditions upon which the debt securities may be redeemed, in whole or in part, at our option or at your option;

the form of the debt securities;

any provisions for payment of additional amounts for taxes and any provision for redemption, if we must pay such additional amounts in respect of any debt security;

the terms and conditions, if any, upon which we may have to repay the debt securities early at your option;

the currency, currencies or currency units for which you may purchase the debt securities and the currency, currencies or currency units in which principal and interest, if any, on the debt securities may be payable;

the terms and conditions upon which conversion or exchange of the debt securities may be effected, if any, including the initial conversion or exchange price or rate and any adjustments thereto and the period or periods when a conversion or exchange may be effected;

whether and upon what terms the debt securities may be defeased;

any events of default or covenants in addition to or in lieu of those set forth in the indenture;

provisions for electronic issuance of debt securities or for debt securities in uncertificated form; and

any other terms of the debt securities, including any terms which may be required by or advisable under applicable laws or regulations or advisable in connection with the marketing of the debt securities.

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

You may present debt securities for exchange and you may present debt securities for transfer in the manner, at the places and subject to the restrictions set forth in the debt securities and the applicable prospectus supplement. We will

provide you those services without charge, although you may have to pay any tax or other governmental charge payable in connection with any exchange or transfer, as set forth in the indenture.

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

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which are treated as having been issued at a discount for U.S. federal income tax purposes will be described in the applicable prospectus supplement.

We may issue debt securities with the principal amount payable on any principal payment date, or the amount of interest payable on any interest payment date, to be determined by reference to one or more currency exchange rates, securities or baskets of securities, commodity prices or indices. You may receive a payment of principal on any principal payment date, or a payment of interest on any interest payment date, that is greater than or less than the amount of principal or interest otherwise payable on such dates, depending on the value on such dates of the applicable currency, security or basket of securities, commodity or index. Information as to the methods for determining the amount of principal or interest payable on any date, the currencies, securities or baskets of securities, commodities or indices to which the amount payable on such date is linked and certain additional tax considerations will be set forth in the applicable prospectus supplement.

Certain Terms of the Senior Debt Securities

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

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

the successor entity, if any, is a U.S. corporation, limited liability company, partnership or trust (subject to certain exceptions provided for in the senior indenture);

the successor entity assumes our obligations on the senior debt securities and under the senior indenture;

immediately after giving effect to the transaction, no default or event of default shall have occurred and be continuing; and

certain other conditions are met.

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

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

our default in the payment of principal or premium on the senior debt securities of such series when due and payable whether at maturity, upon acceleration, redemption or otherwise, if that default continues for a period of five days (or such other period as may be specified for such series);

our default in the payment of interest on any senior debt securities of such series when due and payable, if that default continues for a period of 60 days (or such other period as may be specified for such series);

our default in the performance of or breach of any of our other covenants or agreements in the senior indenture applicable to senior debt securities of such series, other than a covenant breach which is specifically dealt with elsewhere in the senior indenture, and that default or breach continues for a

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period of 90 days after we receive written notice from the trustee or from the holders of 25% or more in aggregate principal amount of the senior debt securities of all series affected thereby;

there occurs any other event of default provided for in such series of senior debt securities;

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

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

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

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

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

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

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

The holders of at least a majority in aggregate principal amount of a series of senior debt securities may direct the time, method and place of conducting any proceeding for any remedy available to the trustee or exercising any trust or power conferred on the trustee with respect to such senior debt securities. However, the trustee may refuse to follow any direction that conflicts with law or the senior indenture, that may involve the

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trustee in personal liability, or that the trustee determines in good faith may be unduly prejudicial to the rights of holders of such series of senior debt securities not joining in the giving of such direction and may take any other action it deems proper that is not inconsistent with any such direction received from holders of such series of senior debt securities. A holder may not pursue any remedy with respect to the senior indenture or any series of senior debt securities unless:

the holder gives the trustee written notice of a continuing event of default;

the holders of at least 25% in aggregate principal amount of such series of senior debt securities make a written request to the trustee to pursue the remedy in respect of such event of default;

the requesting holder or holders offer the trustee indemnity satisfactory to the trustee against any costs, liability or expense;

the trustee does not comply with the request within 60 days after receipt of the request and the offer of indemnity; and

during such 60-day period, the holders of a majority in aggregate principal amount of such series of senior debt securities do not give the trustee a direction that is inconsistent with the request.

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

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

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

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

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

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

With respect to the first and second bullet points, only our obligations to compensate and indemnify the trustee and our right to recover unclaimed money held by the trustee under the senior indenture shall survive. With respect to the third bullet point, certain rights and obligations under the senior indenture (such as our obligation to maintain an office or agency in respect of such senior debt securities, to have moneys held for payment in trust, to register the transfer or exchange of such senior debt securities, to deliver such senior debt securities for replacement or to be canceled, to compensate and indemnify the trustee and to appoint a successor trustee, and our right to recover unclaimed money held by the trustee) shall survive until such senior

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debt securities are no longer outstanding. Thereafter, only our obligations to compensate and indemnify the trustee and our right to recover unclaimed money held by the trustee shall survive.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Certain Terms of the Subordinated Debt Securities

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

Subordination. The indebtedness evidenced by the subordinated debt securities is subordinate to the prior payment in full of all our Senior Indebtedness, as defined in the subordinated indenture. During the continuance beyond any applicable grace period of any default in the payment of principal, premium, interest or any other payment due on any of our Senior Indebtedness, we may not make any payment of principal of, or premium, if any, or interest on the subordinated debt securities. In addition, upon any payment or distribution of our assets upon any dissolution, winding up, liquidation or reorganization, the payment of the principal of, or premium, if any, and interest on the subordinated debt securities will be subordinated to the extent provided in the subordinated indenture in right of payment to the

prior payment in full of all our Senior Indebtedness. Because of this subordination, if we dissolve or otherwise liquidate, holders of our subordinated debt securities may receive less, ratably, than holders of our Senior Indebtedness. The subordination provisions do not prevent the occurrence of an event of default under the subordinated indenture.

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

all of the indebtedness of that person for money borrowed;

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

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

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

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

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

DESCRIPTION OF PURCHASE CONTRACTS AND PURCHASE UNITS

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

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

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

DESCRIPTION OF WARRANTS

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

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date of the warrants. The applicable prospectus supplement will also describe the following terms of any warrants:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

any redemption or call provisions; and

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

FORMS OF SECURITIES

Each debt security, purchase contract, purchase unit and warrant will be represented either by a certificate issued in definitive form to a particular investor or by one or more global securities representing the entire issuance of securities. Unless the applicable prospectus supplement provides otherwise, certificated securities in definitive form and global securities will be issued in registered form. Definitive securities name you or your nominee as the owner of the security, and in order to transfer or exchange these securities or to receive payments other than interest or other interim payments, you or your nominee must physically deliver the securities to the trustee, registrar, paying agent or other agent, as applicable. Global securities name a depositary or its nominee as the owner of the debt securities, purchase contracts, purchase units or warrants

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represented by these global securities. The depositary maintains a computerized system that will reflect each investor's beneficial ownership of the securities through an account maintained by the investor with its broker/dealer, bank, trust company or other representative, as we explain more fully below.

Registered Global Securities

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

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

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

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

Principal, premium, if any, and interest payments on debt securities, and any payments to holders with respect to warrants, purchase agreements or purchase units, represented by a registered global security registered in the name of a depositary or its nominee will be made to the depositary or its nominee, as the case may be, as the registered owner of the registered global security. None of Alnylam, the trustees, the

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warrant agents, the unit agents or any other agent of ours, agent of the trustees or agent of the warrant agents or unit agents will have any responsibility or liability for any aspect of the records relating to payments made on account of beneficial ownership interests in the registered global security or for maintaining, supervising or reviewing any records relating to those beneficial ownership interests.

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

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

PLAN OF DISTRIBUTION

We may sell securities:

through underwriters;

through dealers;

through agents;

directly to purchasers; or

through a combination of any of these methods of sale.

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

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

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

at a fixed price, or prices, which may be changed from time to time;

at market prices prevailing at the time of sale;

at prices related to such prevailing market prices; or

at negotiated prices.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

LEGAL MATTERS

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

EXPERTS

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

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

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\$150,000,000

**Debt Securities
Common Stock
Preferred Stock
Purchase Contracts
Purchase Units
Warrants**

PROSPECTUS

, 2011

Table of Contents**PART II.****INFORMATION NOT REQUIRED IN PROSPECTUS****Item 14. *Other Expenses of Issuance and Distribution.****

Set forth below is an estimate (except in the case of the registration fee) of the amount of fees and expenses to be incurred in connection with the issuance and distribution of the offered securities, other than underwriting discounts and commissions.

SEC registration fee	\$ 17,415
Printing and engraving	10,000
Accounting services	25,000
Legal fees of registrant's counsel	25,000
 Total	 \$ 77,415

* All amounts except the registration fee are estimated.

Item 15. *Indemnification of Directors and Officers.*

Section 145 of the General Corporation Law of the State of Delaware, or the DGCL, provides, generally, that a corporation shall have the power to indemnify any person who was or is a party or is threatened to be made a party to any threatened, pending or completed action, suit or proceeding (except actions by or in the right of the corporation) by reason of the fact that such person is or was a director, officer, employee or agent of the corporation against all expenses, judgments, fines and amounts paid in settlement actually and reasonably incurred by such person in connection with such action, suit or proceeding if such person acted in good faith and in a manner such person reasonably believed to be in or not opposed to the best interests of the corporation and, with respect to any criminal action or proceeding, had no reasonable cause to believe his or her conduct was unlawful. A corporation may similarly indemnify such person for expenses actually and reasonably incurred by such person in connection with the defense or settlement of any action or suit by or in the right of the corporation, *provided* that such person acted in good faith and in a manner he or she reasonably believed to be in or not opposed to the best interests of the corporation, and, in the case of claims, issues and matters as to which such person shall have been adjudged liable to the corporation, *provided* that a court shall have determined, upon application, that, despite the adjudication of liability but in view of all of the circumstances of the case, such person is fairly and reasonably entitled to indemnity for such expenses which such court shall deem proper.

Section 102(b)(7) of the DGCL provides, generally, that the certificate of incorporation may contain a provision eliminating or limiting the personal liability of a director to the corporation or its shareholders for monetary damages for breach of fiduciary duty as a director, *provided* that such provision may not eliminate or limit the liability of a director (i) for any breach of the director's duty of loyalty to the corporation or its shareholders, (ii) for acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law, (iii) under section 174 of the DCGL, or (iv) for any transaction from which the director derived an improper personal benefit. No such provision may eliminate or limit the liability of a director for any act or omission occurring prior to the date when such provision became effective.

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

Item 16. *Exhibits.*

The exhibits to this Registration Statement are listed in the exhibit index, which appears elsewhere herein and is incorporated herein by reference.

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Item 17. Undertakings.

The undersigned Registrant hereby undertakes:

(1) To file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement:

(i) to include any prospectus required by Section 10(a)(3) of the Securities Act of 1933, as amended, or the Securities Act of 1933;

(ii) to reflect in the prospectus any facts or events arising after the effective date of this registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in this registration statement. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than a 20 percent change in the maximum aggregate offering price set forth in the Calculation of Registration Fee table in the effective registration statement; and

(iii) to include any material information with respect to the plan of distribution not previously disclosed in this registration statement or any material change to such information in this registration statement;

provided, however, that paragraphs (1)(i), (1)(ii) and (1)(iii) do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the Commission by the Registrant pursuant to Section 13 or Section 15(d) of the Securities Exchange Act of 1934, as amended (the Exchange Act), that are incorporated by reference in this registration statement, or is contained in a form of prospectus filed pursuant to Rule 424(b) that is part of this registration statement.

(2) That, for the purposes of determining any liability under the Securities Act of 1933, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at the time shall be deemed to be the initial *bona fide* offering thereof.

(3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.

(4) That, for the purpose of determining liability under the Securities Act of 1933 to any purchaser:

(i) each prospectus filed by the Registrant pursuant to Rule 424(b)(3) shall be deemed to be part of the registration statement as of the date the filed prospectus was deemed part of and included in the registration statement; and

(ii) each prospectus required to be filed pursuant to Rule 424(b)(2), (b)(5), or (b)(7) as part of a registration statement in reliance on Rule 430B relating to an offering made pursuant to Rule 415(a)(1)(i), (vii) or (x) for the purpose of providing the information required by Section 10(a) of the Securities Act of 1933 shall be deemed to be part of and included in the registration statement as of the earlier of the date such form of prospectus is first used after effectiveness or the date of the first contract of sale of securities in the offering described in the prospectus. As provided in Rule 430B, for liability purposes of the issuer and any person that is at that date an underwriter, such date shall be deemed to be a new effective date of the registration statement relating to the securities in the registration statement to which that prospectus relates, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof. *Provided, however*, that no statement made in a registration statement or prospectus

that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of contract

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of sale prior to such effective date, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such effective date.

(5) That, for the purpose of determining liability of the Registrant under the Securities Act of 1933 to any purchaser in the initial distribution of the securities, the undersigned Registrant undertakes that in a primary offering of securities of such undersigned Registrant pursuant to this registration statement, regardless of the underwriting method used to sell the securities to the purchaser, if the securities are offered or sold to such purchaser by means of any of the following communications, such undersigned Registrant will be a seller to the purchaser and will be considered to offer or sell such securities to such purchaser:

(i) any preliminary prospectus or prospectus of such undersigned Registrant relating to the offering required to be filed pursuant to Rule 424;

(ii) any free writing prospectus relating to the offering prepared by or on behalf of such undersigned Registrant or used or referred to by such undersigned Registrant;

(iii) the portion of any other free writing prospectus relating to the offering containing material information about such undersigned Registrant or its securities provided by or on behalf of such undersigned Registrant; and

(iv) any other communication that is an offer in the offering made by such undersigned Registrant to the purchaser.

(6) That, for purposes of determining any liability under the Securities Act of 1933, each filing of the Registrant's annual report pursuant to Section 13(a) or 15(d) of the Exchange Act (and, where applicable, each filing of an employee benefit plan's annual report pursuant to Section 15(d) of the Exchange Act) that is incorporated by reference in this registration statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof.

(7) That, for purposes of determining any liability under the Securities Act of 1933:

(i) the information omitted from the form of prospectus filed as part of the registration statement in reliance upon Rule 430A and contained in the form of prospectus filed by the Registrant pursuant to Rule 424(b)(1) or (4) or 497(h) under the Securities Act of 1933 shall be deemed to be part of the registration statement as of the time it was declared effective; and

(ii) each post-effective amendment that contains a form of prospectus shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof.

(8) To file an application for the purpose of determining the eligibility of the trustee to act under subsection (a) of Section 310 of the Trust Indenture Act in accordance with the rules and regulations prescribed by the Commission under Section 305(b)(2) of the Trust Indenture Act.

Insofar as indemnification for liabilities arising under the Securities Act of 1933 may be permitted to directors, officers and controlling persons of the Registrant pursuant to the indemnification provisions described herein, or otherwise, the Registrant has been advised that in the opinion of the Commission such indemnification is against public policy as expressed in the Securities Act of 1933 and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the Registrant of expenses incurred or paid by a director, officer or controlling person of the Registrant in the successful defense of any action, suit or proceeding) is

asserted by such director, officer or controlling person in connection with the securities being registered, the Registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act of 1933 and will be governed by the final adjudication of such issue.

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Table of Contents**SIGNATURES**

Pursuant to the requirements of the Securities Act of 1933, as amended, the Registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this Registration Statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Cambridge, Commonwealth of Massachusetts, on this 21st day of July 2011.

ALNYLAM PHARMACEUTICALS, INC

By: /s/ John M. Maraganore

Name: John M. Maraganore, Ph.D.

Title: Chief Executive Officer

SIGNATURES AND POWER OF ATTORNEY

We, the undersigned officers and directors of Alnylam Pharmaceuticals, Inc. hereby severally constitute and appoint John M. Maraganore and Michael P. Mason, and each of them singly, our true and lawful attorneys with full power to any of them, and to each of them singly, to sign for us and in our names in the capacities indicated below the Registration Statement on Form S-3 filed herewith and any and all amendments (including post-effective amendments) to said Registration Statement (or any other registration statement for the same offering that is to be effective upon filing pursuant to Rule 462(b) under the Securities Act of 1933, as amended) and generally to do all such things in our name and behalf in our capacities as officers and directors to enable Alnylam Pharmaceuticals, Inc to comply with the provisions of the Securities Act of 1933, as amended, and all requirements of the Securities and Exchange Commission, hereby ratifying and confirming our signatures as they may be signed by our said attorneys, or any of them, to said Registration Statement and any and all amendments (including post-effective amendments) thereto.

Pursuant to the requirements of the Securities Act of 1933, as amended, this Registration Statement has been signed by the following persons in the capacities and on the dates indicated.

Signature	Title	Date
/s/ John M. Maraganore John M. Maraganore, Ph.D.	Chief Executive Officer and Director (Principal Executive Officer)	July 21, 2011
/s/ Michael P. Mason Michael P. Mason	Vice President of Finance and Treasurer (Principal Financial and Accounting Officer)	July 21, 2011
/s/ John K. Clarke John K. Clarke	Director	July 21, 2011
/s/ Victor J. Dzau Victor J. Dzau, M.D.	Director	July 21, 2011

/s/ Marsha H. Fanucci	Director	July 21, 2011
Marsha H. Fanucci		
/s/ Steven M. Paul	Director	July 12, 2011
Steven M. Paul, M.D.		

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Signature	Title	Date
/s/ Paul R. Schimmel Paul R. Schimmel, Ph.D.	Director	July 21, 2011
/s/ Phillip A. Sharp Phillip A. Sharp, Ph.D.	Director	July 11, 2011
/s/ Kevin P. Starr Kevin P. Starr	Director	July 21, 2011

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Exhibit No.	Description
1*	Form of Underwriting Agreement
3.1	Restated Certificate of Incorporation of the Registrant (filed as Exhibit 3.1 to the Registrant's Quarterly Report on Form 10-Q filed on August 11, 2005 (File No. 000-50743) for the quarterly period ended June 30, 2005 and incorporated herein by reference)
3.2	Amended and Restated Bylaws of the Registrant (filed as Exhibit 3.4 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
4.1	Form of Senior Indenture
4.2	Form of Subordinated Indenture
4.3	Form of Senior Note
4.4	Form of Subordinated Note
4.5*	Form of Warrant Agreement
4.6*	Form of Purchase Contract Agreement
4.7*	Form of Unit Agreement
4.8	Rights Agreement dated as of July 13, 2005 between the Registrant and EquiServe Trust Company, N.A., as Rights Agent, which includes as Exhibit A the Form of Certificate of Designations of Series A Junior Participating Preferred Stock, as Exhibit B the Form of Rights Certificate and as Exhibit C the Summary of Rights to Purchase Preferred Stock (filed as Exhibit 4.1 to the Registrant's Current Report on Form 8-K filed on July 14, 2005 (File No. 000-50743) and incorporated herein by reference)
5.1	Opinion of Wilmer Cutler Pickering Hale and Dorr LLP
12	Computation of Consolidated Ratios of Earnings/Deficiencies to Fixed Charges
23.1	Consent of PricewaterhouseCoopers LLP
23.2	Consent of Ernst & Young LLP, Independent Auditors of Regulus Therapeutics Inc.
23.3	Consent of Wilmer Cutler Pickering Hale and Dorr LLP (included in Exhibit 5.1)
24.1	Powers of Attorney (included in the signature pages to the Registration Statement)
25.1**	The Statement of Eligibility on Form T-1 under the Trust Indenture Act of 1939, as amended, of the Trustee under the Senior Indenture
25.2**	The Statement of Eligibility on Form T-1 under the Trust Indenture Act of 1939, as amended, of the Trustee under the Subordinated Indenture

* To be filed by amendment or by a Current Report on Form 8-K.

** To be filed pursuant to Section 305(b)(2) of the Trust Indenture Act of 1939.